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Review Article

Cell biological basis of tumor relapse and recurrence – A help from yeast quiescent biology and neuronal quiescent cell biology

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ABSTRACT

Cancer recurrence is initiated by the drug resistance quiescent cells (DRC). The anticancer treatment eliminates cells in the cell cycle (G_1/S/G_2/M), which is drug-sensitive (DSCs) whereas the quiescent (G_0) cells are drug-resistant. It is for this reason, understanding quiescent (G_0) cell biology is critical for dealing with recurrence of cancer. Sensitization (SS) is a process by virtue of which transition of G_0 to drug-sensitive state is done artificially so that recurrence is minimized. In this review, the data were extracted from NCBI, PubMed literature search option which was analyzed and subsequently interpreted by combining principles of cancer therapy, quiescent biology, and neurobiology. In this review, a novel hypothesis is being presented regarding existence of different subtypes of G_0 in human tumor cells (G_{01}, G_{02}, G_{03} …. G_{0n}). Second, a new hypothesis is proposed which might be responsible for existence of heterogeneous cell types in the tumor tissue as observed in early embryonic neuronal biology. The morphogen gradient in the form of signaling molecules secreted from the source activates transcription factors and further interplay between these transcription factors in the different permutation and combination upregulate genes and thus generate cell diversity. It is likely that same kind of mechanism might be in action during development and maturation of tumor generating heterogeneous cell types in the tumor. Third, a few potential novel sensitization agents are being proposed here has been proposed here which is open for further investigation which includes c Myc, Dyrk1B, MARCKS, cycMs3, ERK,p38, HBx, and MT5 which could pave the way for better therapeutic strategy for the treatment of recurrence of the tumor.

Keywords: Cell cycle dynamics, Adjuvant treatment, Cell diversity, Tissue-specific stem cells, Heterogeneous cell types

INTRODUCTION

In this review, data from different species and cell types were extracted, and extensive literature search was done from NCBI, data were re-interpreted and extracted specific to (G_0) biology to compare and document species-specific similarities and differences in human and *Saccharomyces cerevisiae*.[1-11] Like yeast, mammalian or human subjects have been proposed to be having different states of G_0 having unique molecular signature [See Figure 1]. In addition, neuronal developmental theory for generation of tissue diversity (morphogen gradient theory)[12] is being proposed that can be applied as an explanation for cell diversity in the tumor tissue. Sensitization (SS) is a process by which drug resistance quiescent cells are converted to drug-sensitive states which primarily is inside the cell cycle. The term sensitization is intermittently used along with adjuvant treatment.[13] Adjuvant treatment could be used as pre-anticancer therapy agent or post-anticancer therapy

agent. In this review, the sensitization agents proposed are strictly pre-anticancer therapy agents which are one of the new strategies for eliminating the process of recurrence of the tumor. As the process of sensitization is still in its infancy in the field of anticancer therapy, standardization and studying novel factors in the both single-gene level (genes involved in transition of G_0 cells to G_1 phase) as well as in global level (RNA Seq, Exon Array) would help the scientist and clinicians to re-evaluate the anti-cancer therapeutic course including the process of sensitization.

RESULTS AND DISCUSSION

All cancer stem cells (CSCs) are quiescent cells, including tissue-specific stem cells, but not all quiescent cells are CSCs.

In the field of cell biology, different terminologies are used to characterize quiescent cells and proliferative cells, which become confusing for the readers to understand and interpret. As understanding the basic concepts related to quiescent biology used in the literature would pave the way for better coordination among researchers, clinicians, and statisticians studying cancer therapy, quiescent biology as well as researchers focused on investigating different animal models and tissue culture system. The CSCs, normal stem cells (NSC), tissue-specific stem cells are drug-resistant cells which primarily remains in the quiescent state and hence heterogeneous in nature [Figures 1 and 2].[14] So being in a drug-resistance state and at the same time being in quiescent state makes both the subfields interlinked with each other which is important for the researchers in both the fields to evaluate. Tumor cells exist in a dynamic pattern which becomes difficult for the researcher and clinicians to define, categorize and design potential sensitization agents and chemotherapeutic anticancer agents. Hence, it is important to identify and characterize different subtypes of cells present in the tumor tissue. Lacking clarity of the presence of different subtypes of cells in the tumor hinders the process of designing proper and appropriate sensitization agents and its eventual failure in the form re-emergence of the tumor after the anticancer therapy treatment. It is the additional layer of complexity which quiescent cells show from different tissue which demands for further investigation in terms of its genomic and proteomic profile in single-cell level. It is the tissue-specific differences [See Figure 2] along with the species-specific differences along with the transient nature of quiescent state in the tumor tissue derail the drug treatment procedure which results in more generalized kind of approach for the treatment. Uniform codes should be named, defined, and characterized for using multiple terminologies for the same concept or different cell types which scientists, researchers, and drug development companies can use and can coordinate. For CSCs, NSCs, tissue-specific stem cells, and quiescent cells share for being drug-resistant cells with classical G_0 phase of the cells in the cycle, but huge differences might be existing in terms of its epigenetic profile, genomic profile, RNA content, etc. Hence, genome-wide analysis of these cell types should be documented, and data base should be created so that different stakeholders in the cancer therapy field can cross-talk and discuss in the forum which would make the field more interdisciplinary and productive.

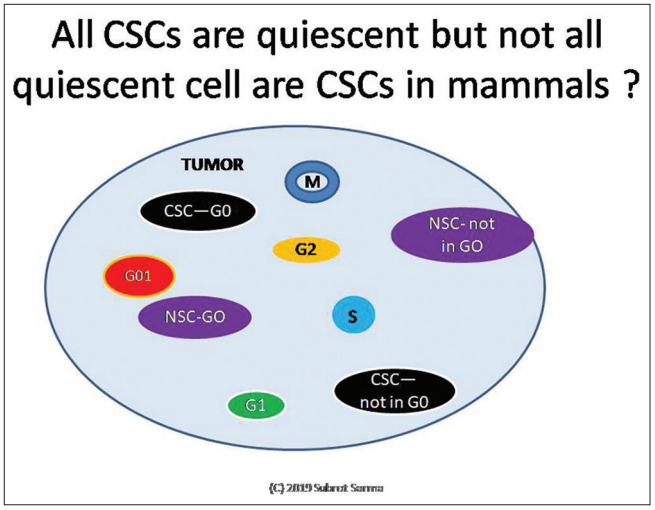

Figure 1: Heterogenous complexity of the Quiescent cells shown with the help of the schematic representation of tumor tissue. Cells in the Tumor tissue ranging from inside the cell cycle (S,M,G2,G1) to quiescent cells(G0). Some CSC remains in quiescent state and others inside the Cell Cycle whereas within the tumor tissue NSC existing in both quiescent and cell cycle state reflecting the complexity of the tumor tissue and problems associated for designing appropriate sensitization agent (See Abbreviations).

Mechanistic view of antimitotic anticancer agents

In this review, the emphasis is on the process of sensitization which is a pre-anticancer therapy process. To gain insight into the mechanistic process of sensitization, the overview of the presently used post-sensitization anticancer therapy might help us to design better strategic plan for pre-anticancer therapy process (sensitization). The drugs commonly used for anticancer therapy include Paclitaxel, Vinblastine, epothilones, and ixabepilone involved in inhibition or activation of microtubule assembly[15] and drugs such as Peloruside A and laulimalide involved in pre-clinical trials.[16] As this review is more focused on the sensitization process from cell cycle perspective in converting drug-resistant cells to drug-sensitive state, so details about antimitotic function and mechanism for anticancer therapy are beyond the scope of this review. Just for information concept of primary resistance comes from genetic alteration of the cells before the anticancer therapy initiates while secondary resistance comes from the cells after the first chemotherapy or whatever treatment is given.[17] Briefly, the mechanisms associated with both primary and secondary drug resistance include suppression of

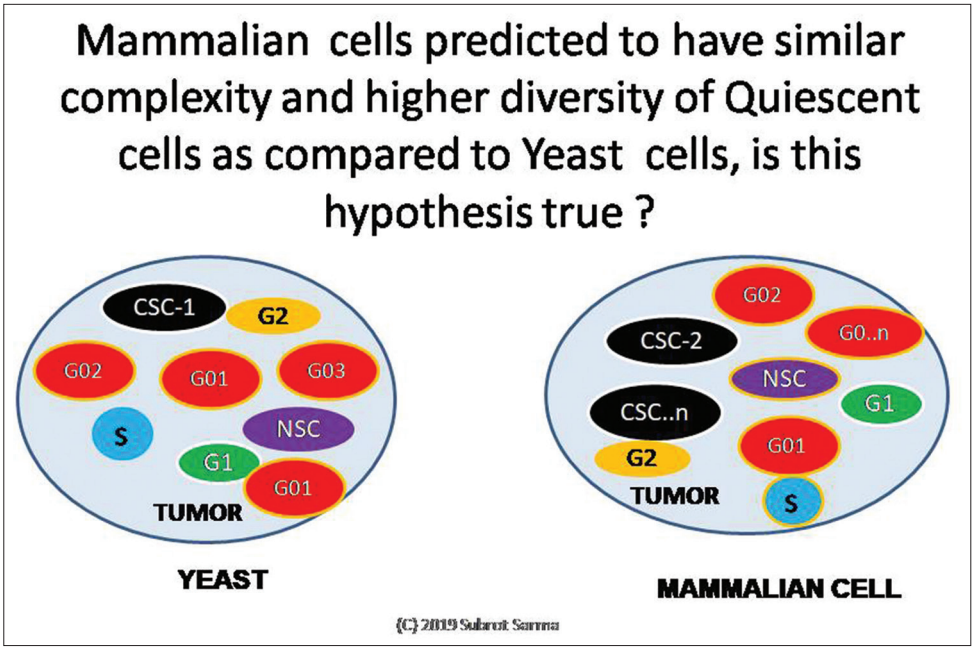

Figure 2: Schematic representation of Heterogenous nature of Tumor tissue in Yeast and Human subjects. Tumor tissue having wide variety of cell types ranging from cells in the Cell cycle (G1/S/G2/M) to variety of quiescent cells. Normal stem cells (NSCs), Tissue specific cell (e.g., NSC, Neuronal Stem Cells). Predicting presence of multiple Quiescent cells (G01, GO2,GO3...GOn) in both yeast and Mammals- species specific differences or difficulty in resolving or detection with already available microscopic techniques.

apoptosis, gene amplification, epigenetic changes, improving DNA-repair mechanism, inactivation anticancer drugs, ABC transporters, reduction in the absorption of drug, blocking of apoptosis, alteration of drug metabolism, and microRNA gene silencing.[18-40] The field of cancer therapy focuses on the antimitotic part of the treatment effectively, but the sensitization part which deals with recurrence or relapse has not got the attention it should get and so, in this review, it is small effort to bring attention to the sensitization part of the treatment from the cell cycle perspective.

Anticancer treatment with or without sensitization process

Conventionally, the anticancer treatment relies on the antimitotic activity of the drug in the scheme of anticancer therapy.[41] The tumor tissue consists of different cell types depending based on the stage of the cell cycle such as G_1/S/G_2/M, Quiescent cells (G_0), NSCs, CSCs, and depending on the type of tissue (e.g., brain cancer cells). The drug treatment manages to eliminate the cells in the cell cycle while rest of the cells are drug-resistant based on its ability to transition to the quiescent state [Figures 3 and 4]. After the therapy stops, the quiescent cells enter the cell cycle and recurrence of the tumor takes place [Figure 3].

There are two alternative ways; the problem can be resolved depending on the context. First, eliminate the quiescent cells directly by use of a combinational approach (chemotherapy followed by surgery or hormonal therapy in case of breast cancer) before the actual antimitotic anticancer treatment which is a difficult task since these cells are primarily drug-resistant. Alternatively, force the quiescent cells to enter the cell cycle which in a way mean forcing the drug-resistant cells to drug-responsive state, a process defined as sensitization so that maximum cells get eliminated after the sensitization process and not enough cells remain for the revival of tumor which means slow rate of tumor relapse and subsequent longer lifespan. This process eliminates the origin of the tumor relapse and that is why the process of sensitization and its design frame (which agents, what cell type, dosage level, etc.) is very critical in the successful completion of the therapeutic program. For this process of sensitization (through cell cycle approach) to be useful, understanding the quiescent cell biology is crucial as quiescent cells are the cell biological basis for designing sensitization agents against the drug-resistant quiescent cells. In contrast, the traditional anticancer therapy without sensitization process, the rate of recurrence of the tumor is very high and that is why sensitization process should be made mandatory in the management of the cancer treatment.

The process of using sensitization agents in the cancer therapy

The adjuvant treatment used in the current time can be defined as a combinational use of different approaches

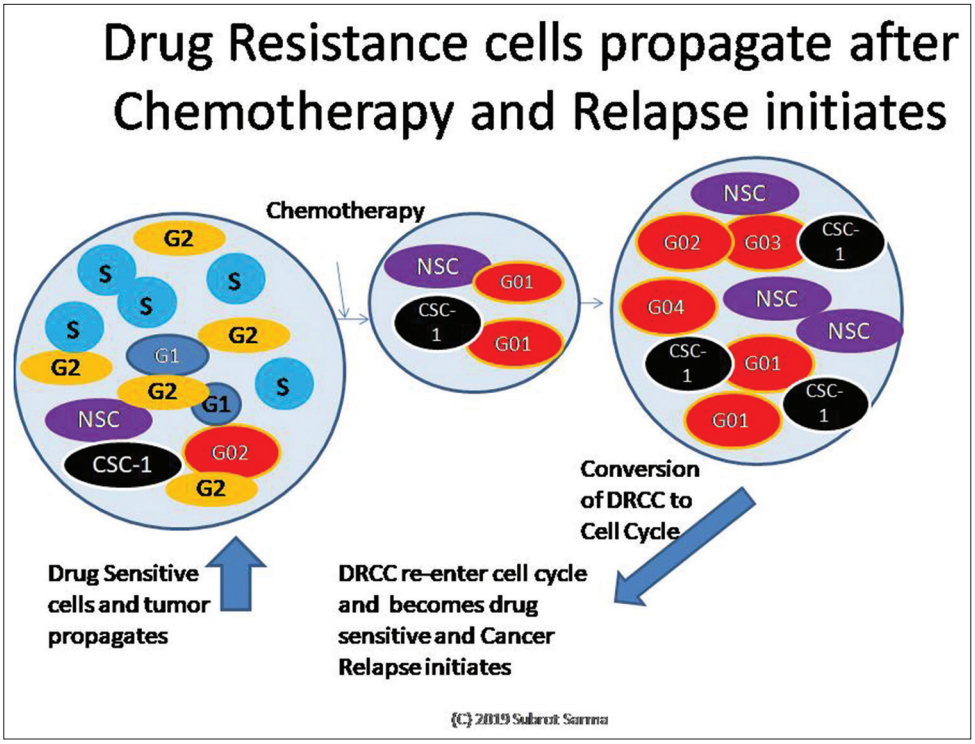

Figure 3: Process of cancer therapy eliminating only cells which are in the cell cycle but drug resistant cells increases gradually after treatment which finally results in tumor relapse.

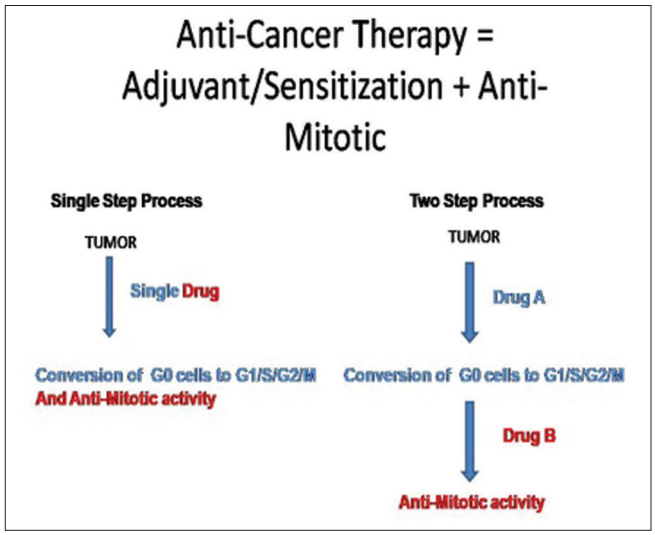

Figure 4: Flowchart shows how with sensitization approach can help us to understand the diseases development and showing how distinction between different steps can improve the full therapy process.

such as surgery, chemotherapy, and hormonal therapy which primarily used after the actual anticancer therapy process. To be specific adjuvant technology is used for frequently along with the anticancer chemotherapy.[42] In the cancer therapeutics, it usually involves different approaches depending on the type of tumor involved as well as stage of the tumor. Adjuvant tamoxifen citrate, adjuvant chemotherapy, and adjuvant radiotherapy[42,43] are few of the established adjuvant technology well characterized in the field of adjuvant treatment. Recently, it has been that reported that PARP inhibitors can be effectively used with chemotherapy or radiotherapy in the treatment of hematopoietic malignancies[44] an enzyme inhibitor of poly ADP-ribose polymerase**.** Other compounds which have got attention to be used as adjuvant in cancer therapy is polyinosinic: Polycytidylic acid and its derivative poly-ICLC as cancer vaccine adjuvants.[45] In the traditional sense, the adjuvant treatment is more of combinational strategy to combat the re-emergence of the tumor using multiple approaches. However, in this review, the proposal is more focused on the pre-anticancer treatment before the actual anticancer therapy could be studied. Hence, giving recognition to the step of sensitization (or cell cycle associated sensitizing agents) would help the researchers and clinicians to completely remove the recurrence of the tumor [Figure 5] shows the prospective cancer therapy scheme using sensitization from the cell biological approach.

One step anticancer therapy and two-step anticancer therapy

Among the drugs used already in the anticancer therapy course which includes adjuvants as well as antimitotic

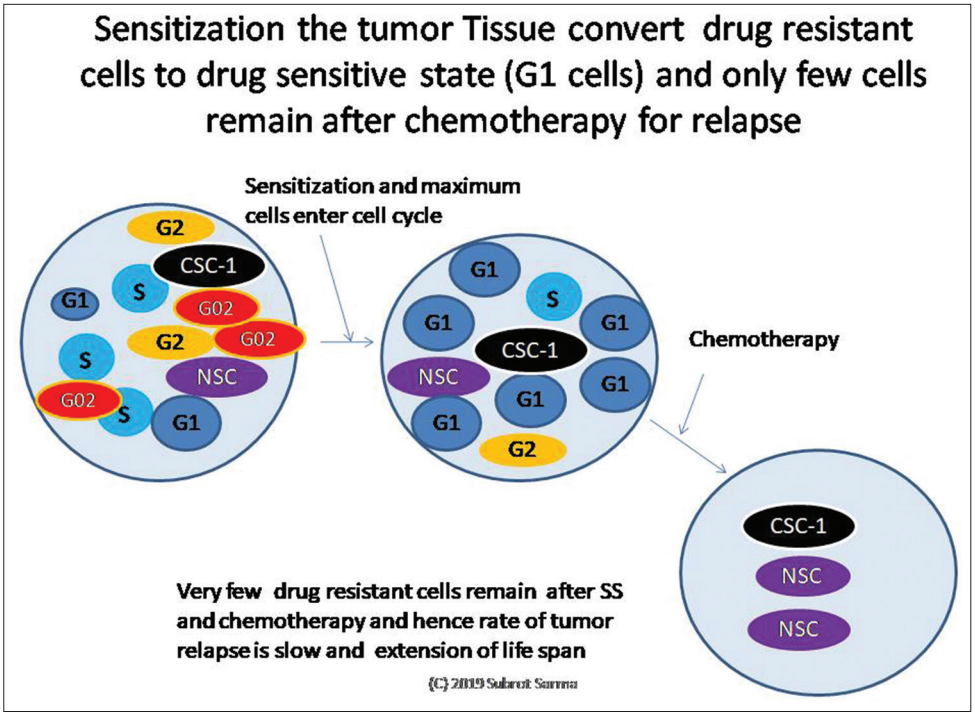

Figure 5: Heterogenous and diverse cell types present in the tumor tissue with added steps of sensitization which result in presence of only few drug resistant drugs as compared to chemotherapy without sensitization, less number of cells available for relapse affecting the recurrence rate and thus increase in the lifespan of the patient. See Table 1 for Abbreviations.

anticancer drugs, identifying potential drug targets that can perform both the sensitization process and antimitotic activity should be investigated. Based on their specific function, the drugs should be categorized based on its ability to force quiescent cells to enter the cell cycle and/or its role in acting as antimitotic agents. This would give rise to the concept of one step cancer therapy and/or two-step anticancer therapy process. Figure 4-shows this process in flowchart. Table 1 listed few of the potential sensitization drug targets from the cell cycle perspective which could be tested in the laboratory set as well as in the clinical trials.

Yeast quiescent biology and its implication in the study of cancer relapse in the clinical setup?

Most of the studies in the cell cycle and quiescent biology has come from the model organism of yeast *Saccharomyces cerevisiae*.[46] In the field of cell cycle studies, yeast has been used extensively for its unique properties such as the presence of nucleus and most of the metabolic and cellular pathways being conserved observed in the human.[46] In the yeast and other animal models, different types of G_0 have been proposed such as senescence and differentiated cells based on the reversibility to enter the cell cycle.[47,48] Although above demarcation is well established apart from tissue-specific differences of different cell types (heart, liver, etc.), differences within a single type of quiescent cells, different states have been proposed in the *Saccharomyces cerevisiae*.[49] Here, the author has proposed that the state of quiescent cells is not a singular event but is a continuum where entry or exit from the quiescent state is under distinct signaling cascade, the factors which are different from normal signaling cell cycle cascade.[49] The cell cycle dynamics in terms of its genetic, cellular pathways are relatively well conserved between yeast and human.[50] It would be tempting to speculate that quiescent cells might be having different states (G_{01}, G_{02}, G_{03}, G_{04}... G_{0n}) in both *Saccharomyces cerevisiae* and the human subjects [Figure 2]. Only a powerful imaging system would be able to detect these different states of G_0 cells. Since the cell cycle duration of *S. Cerevisiae* is very short as compared to human cell cycle duration, it would be more feasible to detect it in human cell lines designed for detection in the advanced microscopy. Single-cell imaging along with RNA Seq data could give us some insight into this proposition of finding different types of G_0 or quiescent cells in both yeast and the human. RNA Seq data would reveal different unique genomic signatures attributed to the differential cell type associated with G_0 cells, which should be investigated in detail. Either way, it would make a case for species-specific differences in the cell cycle dynamics between yeast and human [Figure 2].

The diversity of cells in the non-neuronal tumor is based on a combinational gradient of the transcription factor as shown

in other developmental biology system which includes developing neurons?

The heterogeneous nature of the tumor could be explained on the basis of presence of different subtypes of neurons. To understand the complexity of tumor tissue in terms of its differential cell type, the embryonic developmental system like spinal cord development might give useful information.[51] Morphologically the developmental of spinal cord and its growth along with the presence of different neuronal cell types could be correlated with the development and expansion of the tumor tissue. Both the processes show similarities in terms of its growth at the site of origin as well as presence of signaling source and growth factors, respectively. Both the processes are concentration/dose-dependent processes along with presence of activating and inhibitory components playing a critical role in its basic organization [Figure 6]. Although one is a normal developmental state and other being a diseased state, an independent study using whole-genome approach has shown similarities in the expression profile of genes during early embryonic development to the genes involved in the diseased state (personal communication). Advanced methodologies in the genome level (CRISPR-Cas-9, Exon arrays, RNA Seq) along with conventionally techniques of histology, RNA *in situ* hybridization, immunohistochemistry, RT-PCR, etc., could help us to understand the transition process and factors which could be studied in the laboratory set up as well as in the pre-clinical trials.

As in both the cases different subtypes of cells are generated which create problems during anticancer therapy in the form of drug-resistant cells, explaining tumor initiation and reoccurrence from the developmental biology perspective would help the researchers to innovate new sensitization approach (noble sensitization drug agents) for dealing with the drug-resistant cancer cells with the alternative comprehensive sensitization step in the management of the cancer treatment [Figure 3].

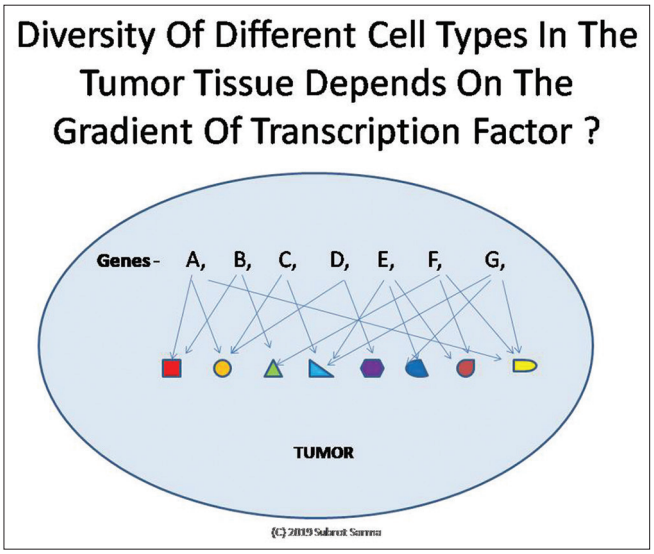

Figure 6: Gradient of the growth factors or other external signals can activate certain genes called transcription factor within the tumor tissue. These transcription via gene interaction in different permutation and combination can generate different cell types in the tumor which makes the drug response of the tumor tissue incoherent and unstable. (A,B, ……..n) are transcription factors under the regulation of external signal (not shown) and different coloured boxes indicating different cell types. Interaction of these transcription factors generates tissue diversity in the tumor.

Table 1: List of potential sensitization agents which could be explored in laboratory and Pre-clinical set-up for anti-cancer therapy.

Genes/Protein	Normal activity	References	Sensitization agent
c-MYC	Master regulator of cell cycle entry- G_1/S transition	[52]	G_0-G_1 transition and possible sensitization agent?
Mirk/Dyrk1B	Kinase	[53]	G_O-G_1 transition
MARCKS	Actin binding protein, myristoylated alaine –rich Kinase	[54]	Expressed only in quiescent cells so good candidate gene sensitization agent –knock down approach
CycMs3	B- type ALFALFA Cyclin Gene	[55]	Over expression might be used for G_0-G_1 transition
LIFR:STAT3: SOCS3 pathway	Maintaining cell cycle dynamics	[56]	Blocking this pathway forces the cells to enter G_1 from G_0, so good candidate for sensitization
ERK MAPK/p38 MAPK pathway	Their proportion of balance between ERK or p38 determine if the cells remain G_0 or it enter the cell cycle.	[57]	Change in the proportion of p38 and ERK pathway components can force the cell to enter cell cycle so good potential candidate for sensitization
Viral proteins HBx & MT-5	Inhibition of Cell Cycle progression	[58]	Knocking down this genes could force the cells to enter cell cycle

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Declaration of patient consent

Not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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