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Investigating Quiescent Cell Biology and Examining Potential Sensitization Agents for Anti-Cancer Treatment in the Neuronal Cell Line

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Abstract

Cancer is one of the most prevalent diseases affecting people across the globe. From it is the relapse of the cancer which affects maximally from the economic and social perspective. Cancer tumors are heterogeneous in nature in terms of having different cell types residing in the different phases of the cell cycle (G1/S/G2/M) as well as cells in G0 phase or quiescent phase. The cells in the cell cycle are primarily drug sensitive whereas cells in the G0 phase are drug resistant. Once the cancer treatment is stopped, transition of G0 cells to the cell cycle occurs which lead to the relapse of the cancer. The mammalian system would help identifying, designing and formulating potential sensitization agent or drugs.

Keywords: Biology; Potential sensitization; Stock market returns; Anticancer

Abbreviations: SS: Sensitization agent; DRC: Drug Resistant Cells; DSC: Drug Sensitive Cells

Introduction

In the year 2018, according to the World Health Organization (WHO) data, the number of deaths due to the cancer has reduced drastically due to the improved health care management scheme. Although the conventional goal in terms of cancer treatment has been focused on the treatment of primary cancer, the recurrence of cancerous state after the primary treatment has not got the attention it deserves in the management of the diseases. Broadly the process of cancer therapy could be divided into two phases (sensitization process and actual anti-cancer therapy [1].

The Drug Resistance Quiescent Cells (DRC) initiate cancer recurrence. The anticancer treatment kills cells in the cell cycle (G1/S/G2/M), which are Drug-sensitive (DSCs), whereas quiescent (G0) cells are drug-resistant. As a result, understanding quiescent (G0) cell biology is crucial for dealing with cancer recurrence. Sensitization (SS) is a technique that artificially transitions G0 to a drug-sensitive state to reduce recurrence. In this review, data were gathered from NCBI's PubMed literature search option and analysed and interpreted using principles of cancer therapy, quiescent biology and neuroscience. In this review, a unique idea about the existence of various subtypes of G0 in human tumour cells (G01, G02 and G03) is provided [2].

Second, a new concept is offered to explain the presence of heterogeneous cell types in tumour tissue, as seen in early embryonic brain biology. The morphogen gradient, which takes the form of signalling molecules secreted from the source, activates transcription factors and the interplay between these transcription factors in various permutations and combinations upregulates genes, resulting in cell diversity. It is believed that the same mechanism is at work during tumour development and maturation, resulting in diverse cell types in the tumour. Third, a few putative novel sensitization agents have been proposed here that are open for further examination, including cMyc, Dyrk1B, MARCKS, cycMs3, ERK, p38, HBx and MT5, which could pave the way for future research [3].

Fundamentally working with neurons would help us to understand quiescent neuron biology with respect to the different brain tumors. It would be worth asking the question if neuronal quiescent cells are behaving differently as compared to non-neuron quiescent cells or they are identical from the cell cycle perspective. Reduction in the time required of the cancer relapse and possible extension of the lifespan of the cancer patient along with improving the health status of the cancer across the globe are some of the positive outcome which could be predicted from the present investigation [4].

Sensitization (SS) is a process that converts drug-resistant quiescent cells to drug-sensitive states largely within the cell cycle. The term sensitization is occasionally used in conjunction with adjuvant treatment. Adjuvant treatment can be utilised as either a pre- or post-anticancer therapeutic agent. The sensitization agents proposed in this study are purely pre-anticancer therapy agents, which are one of the new ways for preventing tumour recurrence. As the process of sensitization in the field of anticancer therapy is still in its infancy, standardisation and investigation of novel components at both the single-gene (genes involved in the transition of G0 cells to G1) and global levels (RNA Seq, exon array) will benefit scientists and patients. Sensitization is a process by which drug resistant cells are made drug sensitive before the actual cancer treatment initiates. Anti-cancer therapeutic action based on agents acting in the translation and transcription level in the DNA and in the protein level [5-7].

Literature Review

In this review, data from various species and cell types were collected and a thorough literature search from NCBI was conducted. Data were re-interpreted and extracted specifically for (G0) biology in order to compare and describe species-specific similarities and differences in humans and *Saccharomyces cerevisiae*. Yeast, mammalian and human individuals, for example, have been postulated to have discrete states of G0 with distinct molecular signatures. Furthermore, a neural developmental theory for the creation of tissue diversity (morphogen gradient theory) is being presented as an explanation for cell diversity in tumour tissue [8].

This review is focused on the first part of process of sensitization and drug resistance. The question is how this process of relapse could be minimized with better effective strategy so that life span of the cancer patient could be extended for a longer period of time. The post-cancer treatment process where subsequent relapse of the cancer after the therapy is stopped is explained on the basis of the heterogeneous nature by virtue of presence of different cell types in terms of cells in the different stages of the cell cycle (G0, G1, S, G2, M) [9].

The drug resistant quiescent ones once the treatment stops, enter the cell cycle and the process of relapse initiates. Considering the extent of the health and economic burden associated with the cancer management specifically dealing with the cancer relapse/recurrence, it is of urgent need that research and development should focus on improving pre-therapeutic sensitization process of the cancer treatment. This also calls for the up-gradation based on the advent of new biomedical techniques in the approach for the treatment of the cancer focusing on the sensitization process [10].

Before discussing potential differential sensitization approaches used, it's very important to understand the biology of the cancer tissue and its diversity. The critical factor which might play an very important role in the effective elimination and reducing the extent of relapse of the solid cancer would be dependent on the characterization, available knowledge regarding cancer biology and future focus of the research question based on the cell cycle dynamics. Using neuronal cell line as model system, it would not only help treating the relapse of tumors related to the brain but also could be extrapolated to others types of tumor in the body [11].

The available drugs primarily (anti-mitotic) eliminate the cells in the cell cycle but not the G0 cells. The question is how one can force the transition of G0 cells into G1 phase so that maximally the anti-mitotic drugs eliminate the tumor and extent of the relapse gets extended, a process called sensitization. In order to design appropriate sensitization drugs, first the quiescent cell biology has to be well defined. The similarities and differences of the quiescent cell biology of non-neuroal cells *vs.* neuronal cells is not well understood. Additionally the study would be performed in neuronal cell line, direct or indirect impact in the neuron related tumors or tumors related to other tissue could be compared [12].

We are asking the question if neuronal cell cycle dynamics in terms of quiescent cells is different from other cells and depending on the outcome similarity and differences once documented could be useful for future drug design for the sensitization process in the cancer therapy management. Third, coupling and uncoupling of already available sensitization and anti-mitotic drugs along with new potential sensitization drug targets would be investigated (a novel strategy in drug design) so that the sensitization process becomes more efficient. Meta analysis was done using pubmed data already available through the existing literature. Different software were used to check the authencity of the write up and any act of plagiarism and none was found using traditional softwares [13].

Discussion

After referring to multiple references and going through the extensive literature search, the main point of conclusion came as lack of extensive information regarding the sensitization process for the anti-cancer therapy. Available literature about information about the drugs markets mainly focus on its mitotic activity which makes sense for the cells in the cell cycle but not for the cells in the quiescent cells which remain dormant while the therapy is used and are prime reasons for the relapse of the cancer. Sensitization process where quiescent cells gets converted to cell cycle state is something the conventional anti-cancer therapeutic strategy is not being used widely may be because of social, economic reasons or because of lack of understanding to differentiate between these two mutually exclusive events in treatment of the cancer, a process which has been described as uncoupling the process of anti-cancer therapy [14].

The details studies in the yeast genome proposes the presence of different subtypes of the quiescent cells (G01, G02, G03…….). In order to identify potential sensitization agents for the conversion its very important to understand the quiescent biology from cell cycle perspective in the standard mammalian system which could be correlated to the clinical set up. The proposal would also give a glimpse of how quiescent cell biology of neurons is similar or different quiescent biology of non-neuron cells. Reduction in the time required of the cancer relapse and possible extension of the lifespan of the cancer patient along with improving the health status of the cancer across the globe are some of the positive outcome which could be predicted from the present communication [15].

Conclusion

Using neuronal cell line, its tempting to propose and to examine if like yeast, mouse and human cells also shows presence of different subtypes of quiescent cells. Understanding the quiescent cell biology in the mammalian system would help identifying , designing and formulating potential sensitization agent or drugs on its own or in combination (depending on presence of which quiescent subtype, G01, G02, G03 …etc) which can be used and extrapolated to the different types of cancer before the use of actual anti-mitotic drug for the cancer therapy. Since the proposed work could be done in the neuronal cell line, the said analysis might help us to understand brain tumors as well.

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