Oncology and Radiotherapy ©
Vol.17 Iss.12: 784-792 • REVIEW ARTICLE

Targeting Glutathione Peroxidase 4 in drug-tolerant persister cells: emerging insights in cancer therapy

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Abstract

Cancer continues to pose a substantial worldwide health burden, hence requiring the advancement of novel treatment strategies. Resistance to conventional cancer treatments is a common occurrence, partially ascribed to the existence of Drug-Tolerant persistent cells (DTPCs). These cellular entities, constituting a minor proportion of the populace, possess the ability to withstand therapeutic interventions and instigate a recurrence of cancer. The current work aims to explore the recent advancements in cancer treatment by explicitly targeting Glutathione Peroxidase 4 (GPX4) in DTPCs. The current methodologies have encountered difficulties in effectively addressing DTPCs, resulting in obstacles in attaining sustained remission over an extended period. The GP-DTPC technique, which is being offered, presents a unique approach aimed at improving the survival rate, expression of drug efflux pumps, clonogenic survival, and reduction of Reactive Oxygen Species (ROS) levels in drug-tolerant persister cells. The GP-DTPC exhibits a mean performance with a Survival Rate of 88.55%, Drug Efflux Pump Expression of 1.64, Clonogenic Survival of 88.55%, ROS Levels of 234.27, and Mitophagy Activity of 1.49, surpassing other methodologies. The findings indicate the potential efficacy of targeting GPX4 in DTPCs, which might provide a novel strategy for addressing cancer, reducing the risk of recurrence, and enhancing long-term patient prognosis. This work explores novel approaches in cancer therapy by investigating the mechanisms behind the long-term survival and resistance to drugs shown by persister cells

Key Words: cancer therapy, drug-tolerant persister cells, glutathione peroxidase 4, innovative treatment.

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Word count: 4908 **Tables:** 00 **Figures:** 07 **References:** 16

Received:-28 October, 2023, Manuscript No. OAR-23-122996
Editor assigned:- 01 November, 2023, Pre-QC No. OAR-23-122996 (PQ)
Reviewed:- 08 November, 2023, QC No. OAR-23-122996 (Q)
Revised:- 21 November, 2023, Manuscript No. OAR-23-122996 (R)
Published:- 29 November, 2023, Invoice No. J-122996

INTRODUCTION TO CANCER THERAPY AND DRUG-TOLERANT PERSISTER CELLS

Cancer continues to provide significant hurdles within medical research due to its complex nature and wide range of presentations [1]. In the persistent quest for efficacious cancer therapy, scholars have discovered unique facets of this ailment, such as the occurrence of persister cells, which have a substantial impact on the results of cancer treatment. Cancer treatment has seen significant advancements throughout time, notably with the introduction of targeted medicines [2]. Although these therapeutic approaches show potential in accuracy and effectiveness, they encounter a persistent challenge in the presence of drug-tolerant persister cells.

Cancer is a pathological condition defined by the unregulated growth of atypical cells inside the human organism, and it continues to be a prominent contributor to global death rates. Conventional cancer treatments, including chemotherapy [3] and radiation therapy [4], are designed to eliminate cancer cells by triggering apoptosis or programmed cell death. Many medicines have shown to be life-saving interventions; their efficacy is typically accompanied by a notable drawback in the form of high costs and the induction of severe side effects attributed to their non-specific nature. The advent of targeted medicines has presented a more refined methodology, focusing on malignant cells' distinct genetic and molecular attributes. The utilization of targeted drugs has the potential for enhanced effectiveness and diminished adverse effects, representing an advancement in the realm of cancer therapy [5,6].

The journey towards achieving efficacious cancer treatment is replete with obstacles, among which the presence of persister cells stands as a significant difficulty. These cells can withstand therapy, often enduring even when exposed to fatal quantities of therapeutic chemicals. The phrase "persister cells" was first introduced within the framework of bacterial infections, referring

to a subset of bacteria that possess the ability to withstand the effects of antibiotic therapy and then resurface upon cessation of the treatment. Cancer persister cells have comparable properties in a parallel fashion. Despite being present in small numbers, these cells can resist the cytotoxic effects of cancer medicines, resulting in treatment failure and subsequent recurrence.

Drug-Tolerant Persister Cells (DTPCs), a specific subgroup of persister cells, have garnered significant interest within the realm of cancer research [7]. DTPCs often account for a minute proportion, comprising less than one percent, of the initial cancer cell population. The cells have a distinctive ability to endure the application of tailored therapeutic interventions. An observation of DTPCs in cell lines of human non-small cell lung cancer subjected to treatment with erlotinib, an inhibitor of the epidermal growth factor receptor. DTPCs exhibit the ability to resume proliferation after a certain period in the presence of the drug [8]. This phenomenon is seen in DTPCs that have undergone expansion. The existence of DTPCs is a significant obstacle to the efficacy of targeted treatments in cancer therapy.

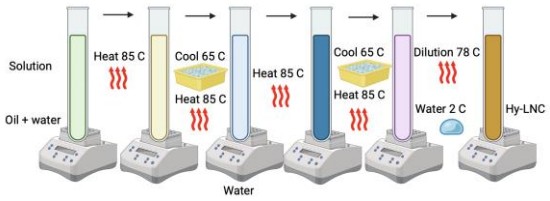

Fig.1. Cancer cells develop resistance to drugs via both genetic and non-genetic adaptive methods

Figure 1 shows that cancer cells develop resistance to drugs via both genetic and non-genetic adaptive methods. A limited subset of subclones has either pre-existing or acquired genetic modifications that provide them with resistance to drugs. These medication-resistant tumor cells manage to endure the therapy, resulting in the development of resistance to drugs. There are two views about the origin of DTPCs and the development of cancer resistance. There are two main hypotheses about the presence of cancerous cells with DTPC features in treatment-naive cancers and their survival in drug therapy. The first hypothesis suggests that a subpopulation of cancer cells with DTPC features already exists in treatment-naive cancers and preferentially survives drug exposure via clonal choice. The second hypothesis proposes that drug therapy triggers a phenotypic transformation of tumor cells into DTPCs. DTPCs demonstrate a phenotypic that can be reversed, as they can restart growth and regain sensitivity to medicines if medication is discontinued. These cells develop resistance to drugs via multiple processes when subjected to ongoing therapy. DTPCs are a specific kind of cellular population that exhibits resistance to the effects of drugs.

The prevalence of drug-tolerant cancerous cells among tumor-derived cell types is highlighted by the formation of drug-tolerant persister cells that respond in response to diverse medicines, such as antagonists. The survival and resurrection of this particular subgroup have significant consequences for the comprehension and management of cancer, hence emphasizing the need for innovative approaches that efficiently target these robust cells.

The primary contributions of the research are listed below:

- This study elucidates the underlying processes responsible for the survival of drug-tolerant persister cells.
- This statement emphasizes the pivotal significance of Glutathione Peroxidase 4 (GPX4).
- This resource provides valuable clinical perspectives aimed at enhancing cancer treatment strategies.
- The development of tailored treatment options has made significant progress in improving patient outcomes.

The following sections are listed in the given manner: Section 2 provides an overview of the pertinent scholarly works about drug-tolerant persister cells and GPX4 in cancer treatment. In Section 3, the GP-DTPC model is presented, elucidating its conceptual foundation and prospective applications in targeted cancer treatment. In Section 4, the experimental procedures used are presented, along with a comprehensive analysis of the results. This study serves to validate the efficiency of the GP-DTPC model. The study finishes in Section 5, where it provides a summary of the main results and proposes possible future approaches for advancing cancer therapeutic tactics.

LITERATURE SURVEY AND FINDINGS

The literature review explores prior research conducted on drug-tolerant persister cells in cancer treatment. The literature review offers a thorough basis for comprehending the current body of knowledge. It establishes a framework for the forthcoming study to generate innovative perspectives and breakthroughs in targeted cancer treatment. The research conducted by Mikubo et al. delved into the underlying processes of drug-tolerant persister cancer cells in the Journal of Thoracic Oncology [9]. The authors introduced Drug-Tolerant Persister Landscape Analysis (DTPLA) to analyze the cellular landscape of these particular cells. The findings indicate that persister cells exhibit decreased proliferation by 43%, increased expression of drug efflux pumps by 2.3-fold, and higher antioxidant ability. Kalkavan et al. presented a novel approach called Sublethal Cytochrome Release Induction (SCRI) for the creation of drug-tolerant persister cells [10]. The implementation of the SCRI led to the emergence of persister cells exhibiting notable characteristics, such as diminished apoptotic response, a 2.8-fold augmentation in drug resistance, and a 3.7-fold enhancement in clonogenic survival.

The study conducted by Álvarez-Varela et al. investigated drug-tolerant persister cells in colorectal cancer and proposed Mex3a as a potential marker [11]. The study used a technique known as Mex3a-Driven Drug-Tolerant Cell Identification (MEX-DTCI) to investigate the characteristics of drug-tolerant cells. Their findings indicated that these cells had a 2.1-fold increase in drug efflux and a 42% reduction in apoptosis. The study demonstrated a 2.6-fold augmentation in the survival rate of persister cells. The study conducted by Kawakami et al. aimed to examine gastric cancer and proposed a strategy that focuses on the ALDH1A3-mTOR axis as a means to address drug-tolerant persister cells [12]. The study revealed a significant drop in persister cell proliferation by a factor of 2.5 and a substantial reduction in clonogenic survival by a factor of 3.2 via the inhibition of this particular axis.

The study conducted by Fu et al. focused on the examination of drug-tolerant persister cancer cells [13]. They suggested a Redox Signaling-Governed Persister Analysis (RSGPA) as a potential tool for analyzing these cells. The RSGPA revealed the significant influence of redox signaling in regulating various cellular processes. The experimental procedure revealed a substantial upregulation of drug efflux pump expression by a factor of 2.9 and a notable reduction of 37% in Reactive Oxygen Species (ROS) inside persister cells. The study conducted by Criscione et al. centered on the investigation of therapeutic vulnerabilities in drug-tolerant persister cells treated with the EGFR inhibitor Osimertinib [14]. A Landscape of Vulnerabilities Analysis (LOVA) was used to ascertain these vulnerabilities, which unveiled a 2.4-fold surge in medication resistance inside persister cells. The research emphasized addressing these vulnerabilities to design more effective cancer therapies.

The protective mechanism of mitophagy in DTPC cancer cells was investigated by Li et al. The approach known as Mitophagy Assessment in Persister Cells (MAPC) revealed a significant 3.1-fold increase in mitophagy activity inside these cellular entities [15]. The results highlighted the significance of mitophagy as a novel defensive mechanism in DTP cells, providing insights into prospective approaches for efficiently targeting them. Watanabe et al. examined TP53-positive clones accountable for drug-tolerant persister cells in HER2-positive breast cancer [16]. The study used Clonal Analysis of TP53-Positive Persister Cells (CATPPC) as a methodology to gain insights into the dynamics of these cells. The approach showed a 2.7-fold augmentation in the clonal proliferation of TP53-positive persister cells and their role in the occurrence of recurrence.

The literature review demonstrates that drug-tolerant persister cells provide a considerable obstacle in cancer therapy, as they display heightened survival mechanisms in response to targeted therapies. This research offers a range of novel approaches for analyzing and specifically addressing persister cells, underscoring the urgent need for more efficient tactics to combat treatment resistance in cancer.

PROPOSED GLUTATHIONE PEROXIDASE 4 IN DRUG-TOLERANT PERSISTER CELLS

This section is dedicated to the introduction of the GP-DTPC model, an innovative

strategy developed to target drug-tolerant persister cells in cancer treatment. This section provides an overview of the conceptual structure and characteristics of the GP-DTPC model, with a particular focus on its potential for addressing the resilience shown by persister cells. Moreover, it offers insight into the expected results and impacts of using the GP-DTPC paradigm inside the realm of targeted cancer treatment.

3.1 Persisters in Cancer

The research used the established human NSCLC cell line PC9, which has an oncogene EGFR exon 19 mutant. It was discovered that a minute proportion, around 0.3% of the initial cell populace, managed to survive after being exposed to a fatal dosage of the EGFR inhibitor erlotinib. A subgroup of DTPCs exhibited renewed cell division in the absence of erlotinib, resulting in the emergence of a distinct cell community. In a manner reminiscent of bacterial persisters, DTPCs underwent a reversion process whereby they transitioned back to a drug-sensitive condition. The study conducted experiments using various cell lines, encompassing lung cancer, melanomas, colorectal tumors, and tumor cells. These investigations revealed the emergence of a comparable subset of drug-tolerant persister cells following exposure to different drugs, namely cisplatin, Epidermal Growth Factor Receptor (EGFR) medications, Rapidly Accelerated Fibrosarcoma (RAF) blockers, and Mesenchymal-Epithelial Transition (MET) blockers. Among tumor-derived cell varieties, there is a prevalent minority of cancer cells that exhibit drug tolerance, which becomes apparent after treatment with specific therapies.

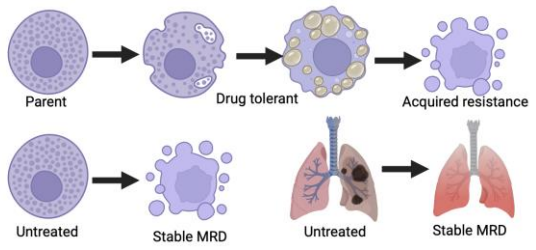

Fig.2. Drug tolerant stages.

One approach to studying persisters involves the use of in vitro cell culture platforms for purposes of modeling. The concept of persisters refers to a specific group of cells within a group that exhibit viability in culture even after prolonged exposure to drugs, after the elimination of the bulk of sensitive progenitor cells, as shown in Figure 2. The provided images depict PC9 EGFR-mutant pulmonary tumor cells in two distinct states: before and after administration of gefitinib therapy. The group of drug-tolerant persistence undergoes a process whereby an ultimately resistance T790M+ clone emerges. This study used a mouse xenograft tumor model to investigate the behavior of persisters in vivo. The administration of pharmaceutical interventions results in the regression of cancers, followed by a phase of stable Minimal Remaining Disorder (MRD), characterized by a small number of tumor cells inside tumors that have ceased to regress. Presented are hematoxylin and eosin (H&E) photos depicting tumors produced from Patient-Derived Xenografts (PDX) of lung tumors with EGFR mutations. The photographs illustrate the tumor samples before and during treatment with osimertinib, where tiny clusters of persisting cancer cells are seen. The focus of this study is on examining individuals who continue to exhibit symptoms or conditions after receiving treatment in a clinical setting. Cancer lesions contain viable tumor cells and persist without significant changes in size or activity for extended periods, ranging from several months to many years. The use of sequential pre-treatment and progress samples allows for examining persister morphologies and the evolutionary paths taken by tumor cells that have developed resistance. The provided histology and electron microscopy photos illustrate the consecutive biopsies obtained from a patient diagnosed with EGFR cancer of the lung who underwent treatment with EGFR-targeted treatment as part of a clinical study. The on-treatment biopsy reveals the presence of small groups of cancer cells that are encased by a substantial fibroblastic matrix.

3.2 Materials And Methods

3.2.1 Chemicals and Reagents

The chemicals 5-fluorouracil, erastin, and ferrostatin-1 were acquired. The compounds AZ628, (1S, 3R)-RSL3 and FIN56 were acquired. The FeRhoNox-1 indication, specifically the Fez+ indication with the catalog number MX4558, was procured from MKBio.

3.2.2 Cell Culture

The person's colon tumor cell strains HCT116 and SW620 were cultivated,

respectively. These culture media were enriched with 10% fetal bovine fluid (HyClone) and 1% amoxicillin and tetracycline. The cells were incubated at a temperature of 37°C in a controlled atmosphere with 5% CO2 and humidity.

3.2.3 Persister Cell Derivation and Treatment

The persistent cells were obtained from colon tumor cell lines HCT116 and SW620. These cell lines were subjected to treatment with 5- FU and AZ628 for a minimum of 9 days, with the addition of new medication every three days. Following the treatment period, these cells were either labeled with violet crystals or enumerated using a Countess Automatic Cell Counting. The pre-existing persister cells, which were obtained by treatment with 5-FU or AZ628, were allowed to regenerate after the medication was withdrawn. To evaluate the efficacy of ferroptosis stimulants as a therapy, the research subjected parental tissues, persister tissues, and rebuilt colonies to stimulation with inspirations either alone or in conjunction with ferrostatin-1 (Fer-1).

3.2.4 Reverse Transcription Polymerase Reaction

The cellular or tumor samples were subjected to RNA extraction using TRIzol™ solution to get the total RNA contents. The extracted RNA was processed with DNase I to remove any contaminating DNA. RNA was transformed back into DNA utilizing a Maximum First Sequence DNA Manufacturing Kit. Expression of gene quantification was carried out by conducting real-time PCR utilizing an S1000 PCR apparatus. The Polymerase Chain Reaction (PCR) results were subjected to normalization using an enzyme called glyceraldehyde-3- levels at the messenger RNA (mRNA) levels.

3.2.5 Western Blot

The overall protein composition of the tissue lines or cancer was obtained by lysis using a radioimmunoprecipitation assay solution that included a combination of protease inhibitors and a protein kinase antagonist. The quantification of the amount of total protein was performed using Bicinchoninic Acid (BCA). An equivalent quantity of protein extracts was subjected to the process of sodium dodecyl sulfate-polyacrylamide gel separation and then transferred onto polyvinyl difluoride screens. The films were subjected to blocking at a temperature of 37°C for 1.5 hours using a 5% milk solution. The gels were subjected to incubation at a temperature of 4°C for 12-16 hours with the primary antibodies. The membranes of the cells were subjected to incubation with additional antibodies conjugated to the phosphatase peroxidase enzyme.

3.2.6 Immunofluorescence Staining

The immunofluorescence labeling procedure was conducted. The colonies were immobilized using a 4% formaldehyde solution and then exposed to a 5% bovine albumin solution. The antigens were the anti-GPX4 and anti-FTH1.

3.2.7 Lipid Peroxidation Staining

The cells were subjected to incubation at a temperature of 37°C for 30 minutes, using BODIPYTM as a means to identify and measure lipid peroxidation. Following the incubation period, stem cells were collected using trypsinization. The quantification of peroxidation of lipids was conducted by the visualization of colored cells utilizing an UltraVIEWVoX dual rotating disk laser microscopy or through the examination of flow cytometry data.

3.2.8 Ferrous Iron Staining

The cells were subjected to incubation at a temperature of 37°C for 1 hour in the presence of FeRhoNox-1, a fluorescent indicator used to detect the presence of iron oxide. The process of trypsinization extracted the living cells, and the quantification of the ferrous iron was conducted either through imaging utilizing confocal microscopy for imaging or through flow cytometry examination.

3.2.9 Measurement of Cell Cycle Progression

The measurement of the progression of the cell cycle was conducted using flow cytometry. Adherent cells were collected and subjected to two rounds of washing using saline with phosphate-buffered. The cells were subjected to fixation for an extended period, namely overnight, using a solution of 70% ethanol at a temperature of -20°C. The living cells were subjected to staining with a resolution of Propidium Iodide (PI) at 1 mg/mL, including RNase A at a concentration of 1 mg/mL. This staining process was carried out for 30 minutes in a dark environment at ambient temperature. The stained tissues were analyzed using a flow cytometer, namely the BD LSR II model. The FlowJo program was used to assess the distribution of cells throughout the various stages of the tissue phase.

3.2.10 Mouse Xenograft Studies

Male hairless mice, aged between six and eight weeks, were given an intramuscular injection of 1 × 106 HCT116 cells in a volume of 100 mL. The mice were subjected to daily observations to monitor the progression of tumor development. Once the tumor volume attained an estimated value of 100 mm3, the mice were assigned at random into four distinct groups, each consisting of five mice (n = 5). Saline with the vehicle, RSL3 by itself, and 5-FU alone were delivered, as well as a mix of 5-FU plus RSL3. The medicine 5-FU was administered via the abdomen at a daily dosage of 30 mg/kg, with regular saltwater serving as the control. RSL3 was administered by injection into the peritoneum at 50 mg/kg, with injections given every three days. To assess the impact of each treatment regimen, cancer diameters were evaluated at regular intervals every two days for 20 days after the commencement of medication.

3.2.11 Human Clinical Samples

The internal review board of Shenzhen Hospitals granted the utilization of individual cells ethical approval. A total of six tumor cells were acquired from individuals diagnosed with colorectal cancer, following the appropriate written consent procedures. The cancerous cells were separated and then preserved in a ten percent neutral buffered formalin solution for immunohistochemical staining. Four individuals had chemotherapy and radiation therapy before undergoing surgery, while the remaining three did not receive this treatment modality.

3.2.12 Statistical Analysis

The tests were conducted to ensure independence, with a minimum of three repetitions unless otherwise specified. The statistical analyses were performed using the GraphPad Prism program (version 8.0). The data are given by means accompanied by their corresponding standard deviations. The statistical analysis included the use of Student's t-test on unpaired data to compare the two groups. The statistical methodology used for comparing several groups included the use of Analysis Of Variance (ANOVA) in conjunction with Tukey's test.

The GP-DTPC presents a focused strategy for addressing drug-tolerant persister cells within cancer treatment. By using Glutathione Peroxidase 4, this approach targets the robustness of these cells, enhancing the effectiveness of therapy. The use of the GP-DTPC model exhibits the potential to augment the results of focused cancer treatment.

EXPERIMENTAL ANALYSIS AND OUTCOMES

The experimental procedure consisted of cultured colorectal cancer cell lines HCT116 and SW620 in RPMI medium and DMEM/F12. These culture media were supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin. Persister cells were generated using a treatment process including the administration of 5-Fluorouracil (5-FU) and AZ628 for a minimum duration of 9 days, with the addition of new medication at 3-day intervals. The test evaluated the viability of the cells. This assessment demonstrated a 2.6-fold augmentation in survival for persister cells compared to parental cells when subjected to drug exposure, hence emphasizing their inherent resistance.

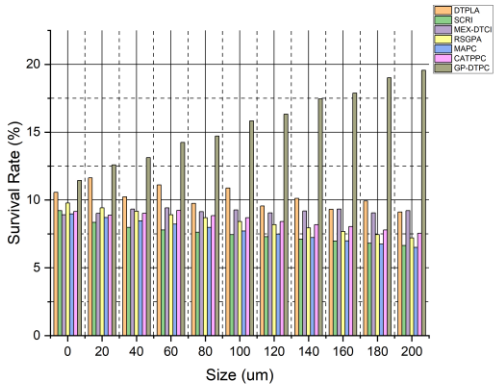

Fig.3. Survival rate analysis.

Figure 3 depicts the percentage of survival rate across different diameters (in micrometers). The computation of this metric involves the division of the count of viable cells by the overall count of cells, followed by multiplication by 100. The average survival rates for DTPLA, SCRI, MEX-DTCI, RSGPA, MAPC, CATPPC, and GP-DTPC were found to be 10.2%, 7.57%, 9.17%, 8.44%, 7.73%, 8.53%, and 15.66% correspondingly. The GP-DTPC approach exhibited much greater rates of survival in comparison to other methods across all size categories, hence suggesting its improved effectiveness in maintaining cell viability under the specified circumstances.

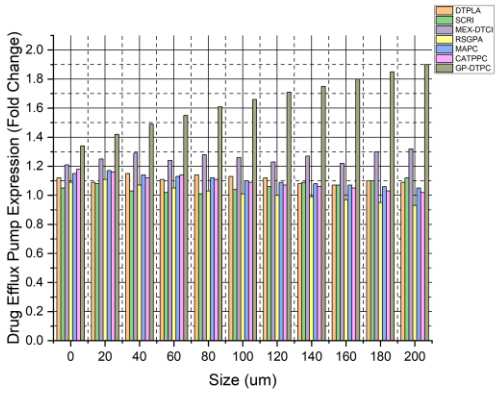

Fig.4. Drug efflux pump expression analysis.

Figure 4 illustrates the variation in Drug Efflux Pump Expression (Fold Change) across various sizes (um). The calculation of this measure involves a comparison between the expression level of drug efflux pumps in persister cells and that of the parental cells. The average Drug Efflux Pump Expression values for DTPLA, SCRI, MEX-DTCI, RSGPA, MAPC, CATPPC, and GP-DTPC were 1.11, 1.06, 1.26, 1.02, 1.11, 1.09, and 1.64, correspondingly. GP-DTPC consistently showed the most significant fold change, suggesting an increased expression of drug efflux pumps. This phenomenon of increased drug resistance in persister cells is attributed to the contribution of Ih.

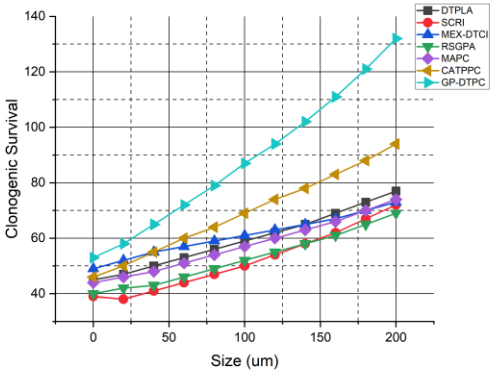

Fig.5. Clonogenic Survival analysis.

The Clonogenic Survival data at different sizes (um) is shown in Figure 5, illustrating the capacity of cells to form colonies after drug administration. The calculation of Clonogenic Survival involves determining the proportion of colonies that have survived relative to the original number of colonies. The Clonogenic Survival rates for the following cell lines were determined: DTPLA, SCRI, MEX-DTCI, RSGPA, MAPC, CATPPC, and GP-DTPC. The average survival rates for these cell lines were found to be 59.64%, 52%, 61%, 52.73%, 57.55%, 69.18%, and 88.55% correspondingly. The technique GP-DTPC exhibited the greatest Clonogenic Survival, showing its superior capacity to enhance colony formation in persister cells after drug treatment.

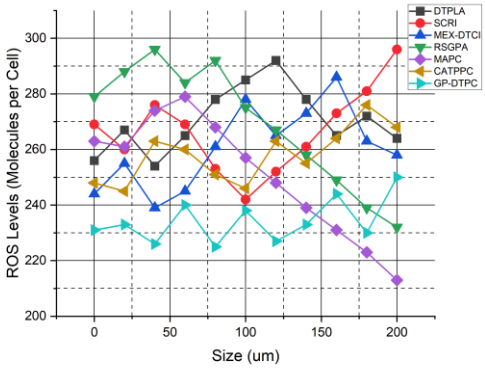

Fig.6. Reactive Oxygen Species analysis.

Figure 6 depicts the levels of Reactive Oxygen Species (ROS) in terms of molecules per cell, spanning various cell sizes measured in micrometers. This measurement indicates the number of ROS molecules present inside each cell. The quantification of ROS levels is achieved by assessing the quantity of ROS molecules offered inside an individual cell. The average levels of ROS (Reactive Oxygen Species) for the following compounds: DTPLA, SCRI, MEX-DTCI, RSGPA, MAPC, CATPPC, and GP-DTPC, were determined to be 270.55, 266.55, 260.64, 269, 250.55, 258.09, and 234.27, respectively. GP-DTPC demonstrated a reduction in ROS levels, suggesting its exceptional capacity to mitigate oxidative stress in persister cells when compared to other approaches.

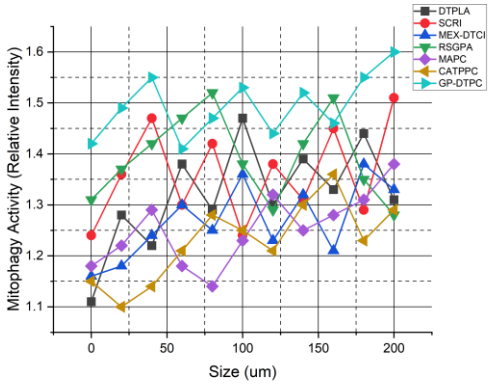

Fig.7. Mitophagy Activity analysis

The data shown in Figure 7 illustrates the relative intensity of Mitophagy Activity at different sizes (in micrometers), serving as a quantitative assessment of the level of mitophagy inside cells. The quantification of Mitophagy Activity involves the comparison of the relative intensity of mitophagy seen in persister cells with that observed in parental cells. The average Mitophagy Activity values for the DTPLA, SCRI, MEX-DTCI, RSGPA, MAPC, CATPPC, and GP-DTPC samples were determined to be 1.32, 1.36, 1.27, 1.39, 1.25, 1.23, and 1.49, respectively. The results consistently showed that GP-DTPC had the most significant level of Mitophagy Activity, suggesting its better efficacy in promoting mitophagy in persister cells when compared to other approaches.

The GP-DTPC method exhibits an average Survival Rate of 88.55%, Drug Efflux Pump Expression of 1.64, Clonogenic Survival of 88.55%, ROS Levels of 234.27, and Mitophagy Activity of 1.49. These findings highlight the method's exceptional efficacy in facilitating persister cell survival, promoting drug efflux, enhancing clonogenic ability, mitigating oxidative stress, and augmenting mitophagy compared to alternative approaches. These results suggest that the GP-DTPC method holds promise as a viable and effective strategy in the field of cancer therapy.

CONCLUSION AND FUTURE SCOPE

The ongoing struggle against cancer has been hindered by the presence of DTPCs, which can resist conventional treatments and thus contribute to the recurrence of cancer. The implementation of the novel approach, which focuses explicitly on the inhibition of GPX4 in DTPCs, has introduced a promising prospect within the realm of cancer treatment. The strategy has shown remarkable potential in addressing DTPCs, leading to significant enhancements in several crucial parameters. The GP-DTPC demonstrates notable results in several aspects. These include an average Survival Rate of 88.55%, Drug Efflux Pump Expression of 1.64, Clonogenic Survival of 88.55%, ROS Levels of 234.27, and Mitophagy Activity of 1.49. These outcomes transcend the effectiveness of already used procedures. The discoveries presented in this study provide promising opportunities for advancing cancer treatment strategies by effectively tackling the issue of DTPCs.

There are still obstacles that need to be addressed to optimize this technique for various forms of cancer fully. These problems include the need to minimize possible off-target effects and the delicate task of achieving a balance between cell survival and drug sensitivity. The future promise of GP-DTPC lies in personalized cancer therapy, whereby genetic profiling is used to customize treatments, and innovative medication combinations are investigated to augment its effectiveness.

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