GSH-Glutathione

https://isom.ca/wp-content/uploads/2020/01/JOM_2001_16_3_10_The_Effect_of_Alternating_Magnetic_Field_Exposure_and-.pdf
The Effect of Alternating Magnetic Field Exposure and Vitamin C on Cancer Cells 2001
The purpose of our study was to examine the anti-tumor effect of vitamin C combined with magnetic field treatments. The inhibitory effect of vitamin C in cancer cells involves its interaction with several compounds: glutathione (GSH), hydrogen peroxide and the enzyme catalase. 17,18 In the blood, vitamin C is oxidized to dehydroascorbate (DHA). DHA is easily transported across cell membranes where it is then reduced by GSH back to vitamin C. Cancer cells have a high level of GSH compared to normal cells. The higher level of GSH for the same level of vitamin C produces more hydrogen peroxide. In normal cells, catalase inactivates hydrogen peroxide by converting it to water and oxygen. Cancer cells have a reduced (10 to 100 fold) intracellular level of catalase. This results in very high levels of hydrogen peroxide and oxidative by-products in the cancer cell. 18 Hydrogen peroxide is toxic and destroys the cancer cells.

https://pubmed.ncbi.nlm.nih.gov/33050144/
Role of Glutathione in Cancer: From Mechanisms to Therapies 2020
Glutathione (GSH) is the most abundant non-protein thiol present at millimolar concentrations in mammalian tissues. As an important intracellular antioxidant, it acts as a regulator of cellular redox state protecting cells from damage caused by lipid peroxides, reactive oxygen and nitrogen species, and xenobiotics. Recent studies have highlighted the importance of GSH in key signal transduction reactions as a controller of cell differentiation, proliferation, apoptosis, ferroptosis and immune function. Molecular changes in the GSH antioxidant system and disturbances in GSH homeostasis have been implicated in tumor initiation, progression, and treatment response. Hence, GSH has both protective and pathogenic roles. Although in healthy cells it is crucial for the removal and detoxification of carcinogens, elevated GSH levels in tumor cells are associated with tumor progression and increased resistance to chemotherapeutic drugs. Recently, several novel therapies have been developed to target the GSH antioxidant system in tumors as a means for increased response and decreased drug resistance. In this comprehensive review we explore mechanisms of GSH functionalities and different therapeutic approaches that either target GSH directly, indirectly or use GSH-based prodrugs. Consideration is also given to the computational methods used to describe GSH related processes for in silico testing of treatment effects.

https://pubmed.ncbi.nlm.nih.gov/29915025/
Glutathione metabolism in cancer progression and treatment resistance 2018
It is crucial to the removal and detoxification of carcinogens, and alterations in this pathway can have a profound effect on cell survival. Excess GSH promotes tumor progression, where elevated levels correlate with increased metastasis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073569/
Glutathione in Ovarian Cancer: A Double-Edged Sword 2018
Given that tumour tissues are highly reducing and hypoxic compared to normal tissues and present higher GSH concentrations [77,78], ...
GSH plays many important roles in cell biology, and evidence suggests that cancer cells are especially dependent on it. Strategies that aim to deplete cellular GSH or target S-glutathionylation of proteins have failed so far. However, exploiting GSH to trigger the delivery of anti-cancer drugs to cancer cells is promising in ovarian cancer treatment.

https://pubmed.ncbi.nlm.nih.gov/23766865/
Role of glutathione in cancer progression and chemoresistance 2013
Glutathione (GSH) plays an important role in a multitude of cellular processes, including cell differentiation, proliferation, and apoptosis, and disturbances in GSH homeostasis are involved in the etiology and progression of many human diseases including cancer. While GSH deficiency, or a decrease in the GSH/glutathione disulphide (GSSG) ratio, leads to an increased susceptibility to oxidative stress implicated in the progression of cancer, elevated GSH levels increase the antioxidant capacity and the resistance to oxidative stress as observed in many cancer cells. The present review highlights the role of GSH and related cytoprotective effects in the susceptibility to carcinogenesis and in the sensitivity of tumors to the cytotoxic effects of anticancer agents.

https://pubmed.ncbi.nlm.nih.gov/31426306/
Targeting Glutathione Metabolism: Partner in Crime in Anticancer Therapy 2019
Targeting glutathione metabolism has been widely investigated for cancer treatment although GSH depletion as single therapeutic strategy has resulted largely ineffective if compared with combinatorial approaches. In this review, we circumstantiate the role of glutathione in tumour development and progression focusing on how interfering with different steps of glutathione metabolism can be exploited for therapeutic purposes.

https://pubmed.ncbi.nlm.nih.gov/33045950/
Glutathione Synthesis in Cancer Cells 2020
Disruptions in GSH synthesis and changes in the GSH/GSSG ratio are common for many pathological conditions, including malignant neoplasms. Numerous data indicate the importance of GSH and the GSH/GSSG ratio in the regulation of tumor cell viability, in the initiation of tumor development, progression, and drug resistance. However, control of the mechanism of GSH synthesis in malignant tumors remains poorly understood.

https://pubmed.ncbi.nlm.nih.gov/22900535/
Glutathione levels in human tumors 2012
Glutathione tends to be elevated in breast, ovarian, head and neck, and lung cancer and lower in brain and liver tumors compared to disease-free tissue. Cervical, colorectal, gastric, and esophageal cancers show both higher and lower levels of tumor glutathione.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11312684/
Glutathione-Dependent Pathways in Cancer Cells 2024
The high GSH/GSSG ratio in tumor cells can be explained by the higher activity of the pentose phosphate pathway (PPP), leading to NADPH(H^+) production
The observed increase in GSH levels is due not only to the higher levels of ROS production in most tumor cells but also to the fact that some of the classical tumor promoters also activate GSH synthesis and turnover mechanisms (e.g., Nrf2) [25,88].
Considering the significant role of GSTs in the processes of malignant growth, the search for their effective inhibitors is underway [231,232].
The increased level of GSH synthesis and expression of GSTP1 in most types of cancer cells, along with a reversed pH gradient (i.e., a lower extracellular pH of ~6.7–7.1 and a higher intracellular pH of 7.4) [271,272], may influence the rate of S-glutathionylation in the tumors.
Numerous data and recent updates demonstrate the significance of GSH and the key GSH-related enzymes in the regulation of tumor cell viability, the initiation of tumor development, its progression, and drug resistance.
As a strategy to counteract cancer progression and therapy resistance, it is promising to search for means of GSH depletion through the inhibition of key enzymes

and/or precursors of its synthesis.

https://rupress.org/jcb/article/217/7/2291/39136/Glutathione-metabolism-in-cancer-progression-and
Glutathione metabolism in cancer progression and treatment resistance 2018
Glutathione (GSH) is an antioxidant that acts as a free radical scavenger and a detoxifying agent in cells. It is useful in a multitude of processes, cellular proliferation, cell division, and differentiation, and is the most commonly elevated metabolite detected during oxidative stress. Under physiological conditions, reduced GSH is the major form present with a concentration 10- to 100-fold higher than the oxidized species (GSH disulfide [GSSG]). Under oxidative stress, GSH is converted by GSH-dependent peroxidases into GSSG upon its reaction with ROS.
With respect to cancer, GSH plays a dual role in its progression. It is crucial in the removal and detoxification of carcinogens, and alterations in this pathway can have a profound effect on cell survival. However, elevated levels of GSH in tumor cells are able to protect such cells in bone marrow, breast, colon, larynx, and lung cancers by conferring resistance to several chemotherapeutic drugs (Wu et al., 2004; Lu, 2009).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11097382/
Glutathione Depletion and Stalwart Anticancer Activity of Metallotherapeutics Inducing Programmed Cell Death: Opening a New Window for Cancer Therapy 2024
The cellular defense system against exogenous substances makes therapeutics inefficient as intracellular glutathione (GSH) exhibits an astounding antioxidant activity in scavenging reactive oxygen species (ROS) or reactive nitrogen species (RNS) or other free radicals produced by the therapeutics. In the cancer cell microenvironment, the intracellular GSH level becomes exceptionally high to fight against oxidative stress created by the production of ROS/RNS or any free radicals, which are the byproducts of intracellular redox reactions or cellular respiration processes. Thus, in order to maintain redox homeostasis for survival of cancer cells and their rapid proliferation, the GSH level starts to escalate. In this circumstance, the **administration of anticancer therapeutics is in vain, as the elevated GSH level reduces their potential by reduction or by scavenging the ROS/RNS they produce**. Therefore, in order to augment the therapeutic potential of anticancer agents against elevated GSH condition, the GSH level must be depleted by hook or by crook. Hence, this Review aims to compile precisely the role of GSH in cancer cells, the importance of its depletion for cancer therapy and examples of anticancer activity of a few selected metal complexes which are able to trigger cancer cell death by depleting the GSH level.
It has been seen that increased levels of GSH detoxify the excessive reactive oxygen species (ROS) or reactive nitrogen species (RNS) and other free radicals produced by the anticancer therapeutics.[14] Thereby, GSH deteriorates the chemotherapeutic efficiency of the drugs.[15]
Plenty of efforts have, therefore, been made over the past few decades to augment the therapeutic efficacy of anticancer drugs by depleting intracellular GSH, as GSH depletion has been validated to recuperate the therapeutic efficacy of ROS-based therapies, viz. photodynamic therapy (PDT), sonodynamic therapy (SDT), chemodynamic therapy (CDT), ferroptosis and chemotherapy.[18−20]
The high level of oxidative stress makes the cells more vulnerable to GSH shortage, creating a lethal weakness. Therefore, tricks to achieve GSH depletion and thereby increase oxidative stress can be successfully applied in cancer therapy.[29]
Therefore, GSH depletion can be assumed to be the key strategy to amplify the oxidative stress in cancer cells, enhancing the destruction of cancer cells by fruitful cancer therapy.
As a consequence, cancer cells are affluent with high antioxidant levels, especially with GSH, whose appearance at an elevated concentration of ∼10 mM (10 times less in normal cells) detoxifies the cancer cells.[45]
Different Strategies for Depleting Intracellular GSH
Based on the different synthetic and metabolic pathways of GSH, strategies for GSH depletion can be grouped into four major points:
(1) eliminating the supply of raw materials for GSH synthesis,
(2) obstructing GSH synthesis and regeneration,
(3) consuming GSH reserves and
(4) promoting GSH efflux (Figure Figure99).
Isothiocyanates (ITC), naturally occurring compounds from cruciferous vegetables, are very familiar for GSH depletion by undergoing conjugation with GSH between the −SH of Cys residues and the highly electrophilic central carbons of ITC.[124,125] Along with the induction of rapid depletion of GSH, ITC is also found to inhibit mitochondrial respiration. Among several reported ITCs, a few, such as β-phenylethyl isothiocyanate (PEITC) and sulforaphane (SFN), were identified to deplete GSH effectively and reached phase II clinical trials for the treatment of oral and lung cancers as well.[126] In addition to this, some reported α,β-unsaturated compounds, such as diethyl maleate (DEM) and phorone (PHO), have also shown a remarkable propensity toward GSH conjugation.[127]
However, applications of transition metal ions have been studied to see if they are the right choice for the permanent consumption of GSH. For example, transition metal ions like iron(III) and copper(II) have been seen to consume GSH permanently through oxidation of GSH and reduction of metal ions. Besides, iron(II) and copper(I) in their reduced states can catalytically reduce molecular oxygen to $O_2^{\bullet-}$ and hydrogen peroxide to $OH^{\bullet}$, which in turn can induce cellular apoptosis and necrosis. Therefore, the oxidation of GSH with transition metal ions can be thought of as the “killing two birds with one stone” strategy in cancer therapy.[129,130]
The main objective of this Review is to highlight the importance of GSH depletion in cancer therapy. Hence, in this section we are going to represent a few examples of metal complexes which have the competency to deplete the intracellular GSH level along with a profound insight into their different GSH-depleting strategies, viz. oxidizing GSH to GSSG, blocking the source of GSH production by forming an adduct with the GSH precursor and being activated by GSH from their inactivated forms, which will be beneficial for destruction of cancer cells by triggering various cell death mechanisms.

https://pubmed.ncbi.nlm.nih.gov/34482088/
Application of glutathione depletion in cancer therapy: Enhanced ROS-based therapy, ferroptosis, and chemotherapy 2021
In cancer cells, a high level of GSH is indispensable to scavenge excessive reactive oxygen species (ROS) and detoxify xenobiotics, which make it a potential target for cancer therapy. Plenty of studies have shown that loss of intracellular GSH makes cancer cells more susceptible to oxidative stress and chemotherapeutic agents. GSH depletion has been proved to improve the therapeutic efficacy of ROS-based therapy (photodynamic therapy, sonodynamic therapy, and chemodynamic therapy), ferroptosis, and chemotherapy.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10452337/
Glutathione: Lights and Shadows in Cancer Patients 2023
It was demonstrated that in cancer, GSH may play a double role according to the different stages (initiation and progression) [19]. In fact, during initiation, GSH counteracts ROS-induced DNA oxidation and DNA damage through a mechanism of elimination of carcinogens by the GSTs [26]. During the progressive stage of cancer, intracellular GSH rates are upregulated to oppose the considerable ROS, thus protecting cancer cells from apoptosis induced by oxidative stress [27].
In cancer cells, the oxidative stress is particularly elevated, so that GSH depletion could make them more susceptible to therapy [28]. In fact, when ROS levels are strategically increased, cancer therapy has shown better results, even if the presence of biological barriers could limit their efficacy. Therefore, one of the therapeutic strategies in cancer should be considered the depletion of the cellular antioxidative systems, among which GSH is one of the main actors [19].

Indeed, in recent years, human clinical research has indicated that nutritional interventions, such as (a) amino acids, (b) omega-3 fatty acids, (c) minerals (i.e., selenium) and vitamins, (d) phytonutrients, (e) green tea, (f) fruit and/or vegetables (i.e., juices), can significantly influence circulating GSH levels.

https://www.sciencedirect.com/science/article/abs/pii/S1773224721007024

Managing GSH elevation and hypoxia to overcome resistance of cancer therapies using functionalized nanocarriers 2022

Therefore, we summarize some of smart nanocarriers for chemotherapy, PDT, and SDT wither alone or combination used to reduce GSH level in TME with simultaneous rise of reactive oxygen species (ROS) levels. Furthermore, overcoming hypoxia and improving PDT could be accomplished by inhibiting hypoxia-induced factor – 1 (HIF-1), which is upregulated in TME, or using nanocarriers that deliver oxygen.

In this regards some investigations have found that depleting glutathione makes cancer cells more sensitive to cisplatin [16] and taxol [17].

The present review explores the recent literature published in the past five years regarding targeting glutathione metabolic enzymes or their synthesis regulators to deplete GSH in cancer. Also, we offer a future perspective on the advantages and limitations of various novel multifunctional nanoparticulate DDSs developed to overcome TME hypoxia and elevated GSH which are the well-defined mechanisms of therapeutics resistance, shading light on nanocarrier based combination chemotherapy.

https://pubmed.ncbi.nlm.nih.gov/32700693/

A simultaneously GSH-depleted bimetallic Cu(ii) complex for enhanced chemodynamic cancer therapy 2020

A bimetallic Cu(ii) complex as a novel antitumor chemodynamic therapy agent with glutathione (GSH) depletion properties is successfully synthesized and well characterized. In tumor cells, the Cu^{2+} ions of the complex are reduced to Cu^{+} ions by GSH and then catalyzed by the overexpressed H_2O_2 to generate highly cytotoxic hydroxyl radicals (˙OH) that kill cancer cells. The complex is quickly taken up by cancer cells and distributed in multiple organelles including mitochondria and the nucleus. The complex demonstrates good cytotoxicity toward various cancer cell lines. However, its toxicity toward normal cells is significantly lower than that toward cancer cells due to the limited expression of H_2O_2. In addition, the complex could arrest the cell cycle of the G0/G1 phase, thereby inducing apoptosis rather than necrosis.

https://pubmed.ncbi.nlm.nih.gov/31602444/

A novel Mn-Cu bimetallic complex for enhanced chemodynamic therapy with simultaneous glutathione depletion 2019

A bimetallic complex, containing Mn(ii) and Cu(ii) moieties, was synthesized for chemodynamic therapy (CDT) of cancer. The complex was capable of generating a hydroxyl radical (˙OH) via a Fenton-like reaction involving a Mn complex, and simultaneously depleting glutathione via a Cu complex induced oxidative reaction, thereby enhancing the efficiency of CDT.

https://pubmed.ncbi.nlm.nih.gov/32227859/

Fusiform-Like Copper(II)-Based Metal-Organic Framework through Relief Hypoxia and GSH-Depletion Co-Enhanced Starvation and Chemodynamic Synergetic Cancer Therapy 2020

The therapeutic effect of traditional chemodynamic therapy (CDT) agents is severely restricted by their weakly acidic pH and glutathione (GSH) overexpression in the tumor microenvironment. Here, fusiform-like copper(II)-based tetrakis(4-carboxy phenyl)porphyrin (TCPP) nanoscale metal-organic frameworks (nMOFs) were designed and constructed for the first time (named PCN-224(Cu)-GOD@MnO_2). The coated MnO_2 layer can not only avoid conjugation of glucose oxidase (GOD) to damage normal cells but also catalyzes the generation of O_2 from H_2O_2 to enhance the oxidation of glucose (Glu) by GOD, which also provides abundant H_2O_2 for the subsequent Cu^{+}-based Fenton-like reaction. Meanwhile, the Cu^{2+} chelated to the TCPP ligand is converted to Cu^{+} by the excess GSH in the tumor, which reduces the tumor antioxidant activity to improve the CDT effect. Next, the Cu^{+} reacts with the plentiful H_2O_2 by enzyme catalysis to produce a toxic hydroxyl radical ($^{\bullet}OH$), and singlet oxygen ($^1O_2$) is synchronously generated from combination with Cu^{+}, O_2, and H_2O *via* the Russell mechanism. Furthermore, the nanoplatform can be used for both TCPP-based *in vivo* fluorescence imaging and Mn^{2+}-induced T_1-weighted magnetic resonance imaging. In conclusion, fusiform-like PCN-224(Cu)-GOD@MnO_2 nMOFs facilitate the therapeutic efficiency of chemodynamic and starvation therapy *via* combination with relief hypoxia and GSH depletion after acting as an accurate imaging guide.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6590529/

Unraveling the Potential Role of Glutathione in Multiple Forms of Cell Death in Cancer Therapy 2019

Growing numbers of studies have implicated that altering the glutathione antioxidant system is associated with multiple forms of programmed cell death in cancer cells.

Afterwards, we also summarize the recent advance in the understanding of the mechanism by which glutathione plays a key role in multiple forms of programmed cell death, including apoptosis, necroptosis, ferroptosis, and autophagy. Finally, we highlight the glutathione-targeting therapeutic approaches toward cancers.

The increased GSH level has been observed in different human cancer cells and is an important contributor to cancer pathology and the resistance to anticancer therapy [7]. As a contrary, GSH depletion increases the susceptibility of cancer cells to various forms of programmed cell death and sensitivity to chemotherapies [8]. Consequently, the role of GSH in the initiation of programmed cell death in cancer cells has been well implicated in accumulative studies.

Cancer cells exhibit a higher ROS level and also develop a greater GSH antioxidant system in order to avoid causing oxidative stress. Programmed cell death, including apoptosis, autophagy, necroptosis, and ferroptosis, is initiated by serials of intracellular programs [59]. In some cases, GSH depletion not only triggers one form of programmed cell death but also may initiate multiple forms of cell death.

Cysteine is the main source for protein synthesis. Undoubtedly, it is of critical importance for maintaining the GSH level.

A reduction in the uptake of extracellular cysteine can directly cause intracellular GSH depletion. Inhibition on xCT expression triggers cysteine starvation and subsequently induces cell growth arrest in cancer cells.

Therefore, regulation of xCT is considered a promising therapeutic target for cancer therapy [135].

Erastin is an inhibitor of system X_c^- that can lead to the depletion of GSH [83]. GSH-depleting effects of erastin could be reversed by supplying with GSH and N-acetylcysteine (NAC).

Sorafenib promotes ferroptosis in HCC cells by its ability to inhibit system X_c^- and deplete GSH [101].

Sulfasalazine is an anti-inflammatory drug which can be used for the treatment of inflammatory bowel disease and rheumatoid arthritis and is also proved to be a potent inhibitor of system X_c^-.

Pseudolaric acid B, a natural diterpene acid isolated from the root and bark of *Pseudolarix kaempferi*, can trigger ferroptosis in glioma cells by depleting cellular GSH through inhibition of xCT [142, 143].

5.2. Inhibition on GCL

γ-GCL plays a key role in the synthesis and maintenance of the cellular GSH level. It is the first and rate-limiting enzyme in GSH synthesis consisting of the GCLC catalytic subunit and GCLM modifier subunit [144]. Overexpression of GCL increases the cellular GSH level, and cells exhibit more resistance to oxidative stress [145].

L-Buthionine-(S,R)-sulfoximine (BSO) is an inhibitor of *γ*-GCL. It has been shown to increase the efficacy of nifurtimox against cancer cells and be an effective modulator of GSH-mediated chemoresistance by increasing the *in vitro* cytotoxicity of alkylating agents and radiation [148].

5.3. Conjugation with GSH

The most direct strategy to deprive GSH is to react with it. Some natural molecules exhibit good affinity to GSH. Sanguinarine directly reacts with cellular GSH and causes a rapid and sever depletion of GSH.

3-Bromopyruvate (3-BP), an alkylating agent, has high reactivity toward thiols and rapidly conjugates with GSH in the cell-free system and many cell types [150, 151]. It has been proved to have antitumor activities [152, 153]. Isothiocyanates (ITCs) are natural phytochemicals abundantly existing in cruciferous vegetables. The central carbon of the ITCs is highly electrophilic and can react with thiols. At physiological pH, ITCs react predominantly with the sulfhydryl group of cysteine residues in GSH. Accumulative evidence has proved that ITCs, such as sulforaphane (SFN), phenethyl isothiocyanate (PEITC), and ally isothiocyanate (AITC), are highly effective in chemoprevention and have antitumor activities in vitro and in vivo [154–158]. PEITC exhibits potential ability against not only solid tumor but also leukemia cells through the rapid deprive of mitochondrial GSH and elevation of ROS [70, 159].

https://pubmed.ncbi.nlm.nih.gov/32917602/

GSH depletion liposome adjuvant for augmenting the photothermal immunotherapy of breast cancer 2020

The high redox level of tumor microenvironment inhibits the oxidation treatment and the immune response. Here, we innovatively develop maleimide liposome (ML) adjuvants to promote immunogenic cell death (ICD) induction and dendritic cells (DCs) maturation by glutathione (GSH) depletion for augmenting the photothermal immunotherapy of breast cancer. The ML effectively depletes the intracellular GSH and up-regulates reactive oxygen species (ROS) in both tumor cells and DCs.