Review Overview of glutathione in cancer

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Abstract

Glutathione is considered as a major molecule that plays an essential role in the antioxidant defense system. The mechanism of chemotherapeutic agents are act based on oxidative stress to kill the cancer cell, so the antioxidant activity of glutathione is thought to be interfering with chemotherapeutic action. Cancer cells could use the glutathione in dual role as protective or pathogenic role based on oxidative stress status. In the current mini review we display how cancer cell benefits from glutathione as antioxidant molecule also we display the previous literature reviews which have demonstrated the linking between glutathione level and oxidative drugs resistance in cancer.

Key words
Glutathione; oxidative stress; cancer; antioxidant; drug resistance.
Introduction

Biochemical background of glutathione

Glutathione (GSH) is a molecule containing a sulfur unit, is composed of three amino acids cysteine, glycine, and glutamine. GSH is considered as the master detoxifier and main antioxidant in the body.[1] The synthesis of GSH from its constituent amino acids depends on two enzymes which include 7-glutamyl cysteine synthetase and glutathione synthetase[2]. There are two forms of glutathione, reduced form (GSH) which represents the majority of GSH, reaching millimolar concentration in the intracellular compartment, and oxidized form (GSSG) which represent less than 1% of the total GSH[3]. Glutathione has important biological functions, these functions include; detoxification, antioxidant defense, maintenance of thiol status, xenobiotic mediated injury and modification of cell proliferation [4][5, 6],[7][8] in addition to that glutathione is able to regenerate the most important antioxidants, Vitamins (C and E,) back to their active forms [9]. Glutathione itself has a complex group of enzymes each enzyme is divided into subunit, but the most enzymes related to glutathione are(i) Glutathione reductase (GR), is a ubiquitous enzyme required for the conversion of oxidized glutathione (GSSG) to reduced glutathione (GSH) [10, 11]. (ii) Glutathione-S-transferase (GSTs), are a family of Phase II detoxification enzymes that catalyze the conjugation of glutathione (GSH) to a wide variety of endogenous and exogenous electrophilic compounds[12]. (iii) glutathione peroxidase (GPx), belongs to a family of phylogenetically related enzymes, GPxs have been known to catalyze the reduction of H2O2 or organic hydroperoxides to water or the corresponding alcohols, respectively, typically using glutathione (GSH) as reductant[13].

all these enzymes are required in maintaining of cell defense mechanism so any alterations in the activities of antioxidant enzymes GR, glutathione peroxidase (GPx), glutathione. S-transferase (GST), may affect the cellular defense system[14].

The role of glutathione in cancer

Regarding cancer, glutathione metabolism is able to play both protective and pathogenic roles [15, 16]. Reactive oxygen species (ROS) are defined as oxygen-containing, reactive chemical molecules. ROS has essential biological functions for instance They regulate signal transduction and modifying the cellular structure of proteins and transcription factors. Under certain condition especially when the level of ROS low or moderate cancer cell may benefit from ROS in invasive and metastases process, but when the level of ROS raised up to the high level it becomes toxic to the cancer cell and lead to oxidative stress situation which makes harmful and killing cancer cells [17]. So at this point cancer cells need to elevate their level of glutathione to overcome oxidative stress status. Then at a low level of glutathione cancer cells become sensitive
to oxidative drugs (pathogenic role) and at a high level of glutathione, cancer cells become resistant to oxidative drugs (protective role).

**Oxidative stress and cancer**

Reactive oxygen species (ROS) normally is produced from metabolic and physiological processes. Under normal circumstances, the harmful effect of ROS is removed through antioxidants either enzymatically or non-enzymatically. But under certain conditions, this balance may be changed when the level of ROS increased over than level of antioxidants balance, then occurs shifts towards the oxidative status and Consequently, oxidative stress, [18]. Most of the oxidative stress occurs in pathological situations, especially during chemotherapy. Generation of ROS is part of the cytotoxic activity of chemotherapy agents as well [19]. Glutathione status reduced glutathione/oxidized glutathione (GSH/GSSG) system can be used to indicate oxidative stress [20][21]. Redox adaptation is an important concept that, to a large degree, explains the mechanisms by which cancer cells survive under persistent endogenous ROS stress and become resistant to certain anticancer agents[22].

The interference of glutathione with the action of chemotherapeutics agents

Drug resistance in cancer chemotherapy represents a major obstacle to the successful treatment of patients with cancer [23]. Chemotherapy acts against cancer cells through an increase in the rate of oxidative stress up to the toxic level to make serious damage in cancer cell large molecules and subsequently cell death [24-28]. But cancer cells create a mechanism to increase their antioxidant rate as a response to the high oxidation rate of chemotherapy [29]. The strength of glutathione as powerful antioxidant molecules attributed to its ability to interrupting the binding of chemotherapeutics agents with cancer cell large molecules and thus cancer cells could escape from killing by chemotherapeutic agents and it becomes more progressive [30].

**The different level of glutathione in cancer patients who undergoing chemotherapy**

A percentage of tumor cells with high GSH content has the ability to survive in the presence of the oxidative stress, thereby it becomes more invasive. Also, the level of GSH has been found elevated in many cancer such as breast tumors and lymph node metastases [31]. Multidrug and radiation resistance of many tumors, as compared with normal tissues, appears to be associated with higher GSH levels in the cancer cells [32]. That means the low level of GSH makes cancer cells more sensitive to killing by oxidative stress. The majority of studies about the changeable level of glutathione in cancer cell have demonstrated that the level of glutathione tends toward increasing and moreover this increasing in the most case associated with resistance to chemotherapeutics agents.

**Conclusion**

Cancer cells have the ability to escape from the toxic effect of most commonly used cancer drugs in spite of their different chemical structures and different mechanisms of intracellular activity. However, drug resistance occurs sooner or later in cancer cells. There are many types of mechanisms could enable cancer cell to escape from chemotherapeutics agents, but the most effective mechanism is antioxidant defense pathway especially through glutathione, because the most harmful effect which occurs to cancer cell, it comes from Reactive Oxygen Species (ROS) which produce from action of chemotherapeutics drugs, so cancer cell needs to elevate its level of glutathione to overcome the oxidative stress situation. So if we could figure out a mechanism to inhibit the antioxidant status in cancer cells then it could be this a forward step toward
overcoming of Drugs resistance and that will benefit patients who suffer from poor response to chemotherapeutics agents.

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**Reference**


