A Paradoxical Chemoresistance and Tumor Suppressive Role of Antioxidant in Solid Cancer Cells: A Strange Case of Dr. Jekyll and Mr. Hyde

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Modulation of intracellular antioxidant concentration is a double-edged sword, with both sides exploited for potential therapeutic benefits. While antioxidants may hamper the efficacy of chemotherapy by scavenging reactive oxygen species and free radicals, it is also possible that antioxidants alleviate unwanted chemotherapy-induced toxicity, thus allowing for increased chemotherapy doses. Under normoxic environment, antioxidants neutralize toxic oxidants, such as reactive oxygen species (ROS), maintaining them within narrow boundaries level. This redox balance is achieved by various scavenging systems such as enzymatic system (e.g., superoxide dismutases, catalase, and peroxiredoxins), nonenzymatic systems (e.g., glutathione, cysteine, and thioredoxin), and metal-binding proteins (e.g., ferritin, metallothionein, and ceruloplasmin) that sequester prooxidant metals inhibiting their participation in redox reactions. On the other hand, therapeutic strategies that promote oxidative stress and eventually tumor cells apoptosis have been explored based on availability of chemotherapy agents that inhibit ROS-scavenging systems. These contradictory assertions suggest that antioxidant supplementation during chemotherapy treatment can have varied outcomes depending on the tumor cellular context. Therefore, understanding the antioxidant-driven molecular pathways might be crucial to design new therapeutic strategies to fight cancer progression.

1. Introduction

Reactive oxygen and nitrogen species (ROS/RNS) are oxidants natural products formed during cell vital metabolism activity that orchestrate the transmission of regulatory signals for proliferation, migration, defence, vasorelaxation, autophagy, and apoptosis signals (Figure 1(a)) [1–12]. Progress in redox biochemistry study has revealed an oxygen adaptation, whereby the cell has acquired the capability to initiate changes to the local redox environment as a means of regulating signaling pathways [1–4, 6–11]. This has changed the way cellular oxidant production is viewed, from a simplistic model where all oxidant production is inherently damaging to a more complex scenario where a regulated small increase in oxidant production can be essential for optimal cellular function (Figure 1) [1–12]. In this model ROS and RNS act as second messengers, forming an integral part of the signal transduction network [1–4, 9, 11, 12]. Reactive nitrogen species are produced by the endothelium inducing vascular relaxation when vascular smooth muscle cells were stimulated with vasodilators such as acetylcholine, histamine, and bradykinin. Nitric oxide synthase catalyzes a five-electron oxidation of a guanidine nitrogen of L-arginine in the formation of citrulline and nitric oxide [7–9, 11, 12]. On the other hand, ROS are heterogeneous group diatomic oxygen derived of free and nonfree radicals species with a wide range of reactivity [10–12]. Their formation begins with the univalent reduction of oxygen to produce superoxide radical (O₂⁻), a free radical that gives rise to many highly reactive species such as hydroperoxyl radical (HO₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radical (·OH) (Figure 2) [10–12]. For example, superoxide can dismutate to form hydrogen peroxide (H₂O₂), a membrane-permeable, mildly prooxidant molecule which in turn can lead to formation of several highly oxidizing derivatives such as hydroxyl radicals (Figure 2). Also, O₂⁻ can react with nitric oxide (NO*) resulting in peroxynitrite (OONO−), a high RNS (Figure 2) [11, 12]. Mitochondria
Central to ROS/RNS production and signaling is their role in physiological conditions, where they contribute to processes such as autophagy, defense, vasorelaxation, and proliferation. Abnormal oxidant production is characteristic of many diseases, leading to extensive tissue damage. Antioxidants play a crucial role in neutralizing these reactive species to prevent oxidative damage.

**Figure 1:** Schematic representation of reactive oxygen and nitrogen species (ROS/RNS) inductions in physiological (a) and pathophysiological (b) conditions.

**Figure 2:** Sources of reactive oxygen (ROS) and nitrogen (RNS) species production. Enzymatic and nonenzymatic antioxidants counterbalance it.

Form the major powerhouse of ROS production; they are generated in association with the activity of the respiratory chain such as NADH dehydrogenase enzyme complexes in aerobic ATP production [13–15]. In addition, two classic phagocytic ROS-generating enzymes use molecular oxygen as a substrate, including the multisubunit NADPH oxidase and its homologue NOX/Duox family and myeloperoxidase in various tissues in response to extracellular influences [16, 17]. Other sources of ROS production include the cytochrome P450 (CYP450) system, which is involved mainly in removing or detoxifying toxic substances in the liver [13] and xanthine oxidase which catalyzes the oxidation of hypoxanthine to xanthine with the formation of $\text{H}_2\text{O}_2$ [18]. The imbalance of this cellular redox state is characteristic of many diseases where abnormal oxidant production causes extensive tissue damage (Figure 1(b)) [3, 6, 19]. Antioxidant has been defined as any substance that significantly delays or prevents oxidative damage of an oxidizable substrate (Figure 2). Due to their high reactivity, the ROS production levels are tightly controlled by antioxidants to avoid oxidative...
stress and, eventually, oxidative damage which is frequently linked to genetic instability, tumor promotion, and metastasis (Figure 1) [20]. On the other hand, the primary mechanism of many chemotherapy drugs and ionizing radiation, widely used against cancer cells, is the formation of ROS [11, 21]. At this point, questions arise whether reduction of oxidative stress in tumor cell environment with antioxidant treatment would be beneficial or not [22]. Moreover, it should be stressed that the antioxidants cannot distinguish between the radicals that play a beneficial role and those that cause carcinogenesis. Understanding the biological redox system for the development of more effective and less toxic chemotherapy ROS induction strategies for cancer cells is deserved [21, 22]. Therefore, the modulation of intracellular antioxidant concentration is a double-edged sword, with both sides exploited for potential therapeutic benefits.

2. ROS and Hypoxia in Solid Tumors

Solid tumors are known to have a poor microvascular network and high interstitial fluid pressure resulting in hypoxic environment conferring chemo and radiotherapy resistance [22]. There are three major forms of hypoxia that varies with the duration: acute, chronic, and intermittent. Acute hypoxia occurs when tumor vessels become temporarily hypoxic for a period of seconds or a few hours. Chronic hypoxia is a progressive and severe reduction in oxygen (hours to days) [22]. Intermittent hypoxia, also referred to as cycling hypoxia, is characterized by cyclic periods of hypoxia and reoxygenation and plays the main role in resistance of solid tumor treatments (Figure 3) [23–26]. Hypoxic microenvironments are characterized by extreme heterogeneities in tumor cells oxygenation that arise as a result of the increased oxygen diffusion distance due to tumor expansion and poorly developed vascular networks [22, 27]. Gradients in oxygen are frequently found surrounding perfused vessels, ranging from normal values near the blood vessel to complete anoxia adjacent to necrosis [27, 28]. The balanced proportion of hypoxic cells in cancer is driven by the tolerance of individual cells to these different types of hypoxia and varies remarkably among different tumors with otherwise similar clinical features [29]. These differences are important, because the fraction of viable hypoxic cells is a major determinant of prognosis, as hypoxic cells are highly resistant to chemotherapy and radiation therapy (Figure 3). Reducing cellular tolerance to hypoxia is therefore a strategy to reduce the proportion of hypoxic cells in tumors to improve current cancer therapy [27–33]. Tumor cells can adapt to hypoxic conditions by employing a variety of survival tools, which result in the promotion of cancer cell growth and metastasis [22, 32]. This adaptation is mainly mediated by hypoxia-inducible factor-1 (HIF-1) (Figure 3). HIF-1 is a heterodimeric transcription factor consisting of an oxygen-regulated subunit (HIF-1α) and a stable nuclear factor, HIF-1β aryl hydrocarbon receptor nuclear translocator (ARNT). Under normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylase (PHD) at proline 402 and proline 564, and the hydroxylated HIF-1α recruits von Hippel-Lindau (pVHL), an E3 ubiquitin protein ligase, and is rapidly degraded by the proteasome after being targeted for ubiquitination (Figure 3). Under hypoxic conditions, cytosolic HIF-1α is stabilized by inhibition of the oxygen- and PHD-dependent enzymatic hydroxylation of proline residues and subsequently translocated to the nucleus, where it binds HIF-1β [30, 34, 35]. The complex binds to the hypoxia-response element in its targets, which results in the transactivation of numerous genes encoding proteins necessary for the blood supply, energy production, growth/survival, invasion/metastasis, and chemo/radioresistance (Figure 4) [30, 35]. An association of HIF-1α overexpression with cell proliferation and poor prognosis has been observed in many kinds of human cancers [30, 34, 35]. It is well known that hypoxic conditions increase intracellular ROS levels [14] and recent studies provide important insights into the molecular mechanisms by which cycling hypoxia increases the oxidative stress [24]. This constant generation of ROS through intensive cycling hypoxia stabilizes HIF-1α by preventing its degradation and induces HIF-2α degradation (Figure 3). Since HIF-2α regulates genes encoding prooxidant enzymes and HIF-2α is a potent regulator of the genes encoding antioxidant enzymes, it was proposed that both HIFs contribute in part to the oxidative stress caused by cycling hypoxia. [36–39]. Ironically, the main mechanism of ionizing irradiation and many anticancer drugs to induce apoptosis is through ROS which activate HIF-1α [11, 30].

3. ROS and Chemotherapeutic Drugs

Despite great improvements in screening strategies and adjuvant therapies, current treatments still rely heavily on conventional chemotherapy for most cancers. Additionally, most of these conventional chemotherapies agents such as taxanes, anthracyclines, and platinum coordination complexes induce ROS [11, 40–42] and are somehow cardiotoxic [43, 44].
Hence, the efficacy of these prooxidant chemotherapeutic agents is dose-dependent, which is limited by toxicity to nontumor tissues, as a result of its poor tumor selectivity. Modulation of ROS levels by antioxidants may be effective in protecting nontumor tissues especially the heart from oxidative damage but they may also reduce the efficacy of these anticancer drugs [43]. Nevertheless, the mechanism by which these chemotherapeutic agents inducers exhibit antitumor effects is likely multifactorial. Consequently, to improve survival length and preserve quality of life, the challenge is to develop approaches aimed at increasing chemotherapy toxicity to tumor tissue while not affecting nontumor tissues [43, 44]. Therefore, the degree to which ROS contribute to the antineoplastic effects of these chemotherapeutic drugs should be evaluated.

4. Antioxidants Playing Hyde and Jekyll

4.1. Exogenous Antioxidant. In order to maintain an appropriate level of ROS and regulate their action, the body’s natural defense against oxidative stress consists of several antioxidative systems. Therefore, mammalian cells have developed many enzymatic and nonenzymatic antioxidative systems [20, 45, 46] as well as transfer proteins that sequester prooxidant metals inhibiting their participation in redox reactions (Table 1) [47]. Components of the endogenous antioxidant defense system work together and in concert with dietary antioxidants (Table 2) [20, 21, 46] to prevent and reduce oxidative stress. In addition, the antioxidant activity of many of these enzymes and compounds is reliant upon minerals derived from the diet such as selenium, copper, manganese, and zinc (Table 2) [48]. Much debate has focused on the use of antioxidant supplements by patients undergoing chemotherapy due to concerns that the antioxidants may interfere with the mechanism of action of the therapeutic agent and subsequently decrease its efficacy [21, 49]. On the other hand, others argue that antioxidant supplements are beneficial to patients undergoing chemotherapy because they enhance the efficacy of the chemotherapy as well as alleviate toxic side effects, allowing patients to tolerate chemotherapy for the full course of treatment and lessen the need for dose reduction [20, 43].

**Table 1: Endogenous antioxidants.**

| Endogenous antioxidants | Examples                      |
|-------------------------|-------------------------------|
| Enzymes                 | Superoxide dismutase          |
|                         | Catalase                      |
|                         | Peroxiredoxins                |
| GSH enzyme-linked system| Glutathione peroxidase        |
|                         | Glutathione S-transferase     |
|                         | Glutathione reductase         |
| Nonenzymes              | Glutathione                   |
|                         | Cysteine                      |
|                         | Thioredoxin                   |
| Metal-binding proteins  | Ferritin                      |
|                         | Metallothionein               |
|                         | Ceruloplasmin                 |

**Table 2: Exogenous antioxidants.**

| Example of exogenous antioxidants | Example                  |
|-----------------------------------|--------------------------|
| Vitamin C                         | Ascorbate/ascorbic acid  |
| Vitamin E                         | Tocopherols, tocotrienols |
| Carotenoids                       | α-carotene, β-carotene, lycopene |
| Polyphenols                       | Flavonols, flavanols, anthocyanins, isoflavones, phenolic acid |
| Trace elements                    | Selenium, copper, manganese, zinc |
been reported in different tumor cells [44, 58–60]. However, of chemosensitization through antioxidant modulation have

4.2.1. Glutathione and Chemoresistance.

...resistance [58]. Contrastingly, these cytoprotective effects of GSH and its precursor N-Acetyl cysteine, since direct administration of reduced GSH has physical and chemical limitations [56, 71]. Among the GSH analogues developed, one (TLK 286), which is in clinical trial phase 3 settings for non-small-cell lung and ovarian cancer, appears to sensitize these tumors to cytotoxic chemotherapies [56]. However, the lack of tumor specificity is still a potential problem.

4.3. Antioxidant and Possible Clinical Benefits. Altogether, it should be recognized that understanding the redox biochemistry differences between normal and cancer cells is essential for the design and development of strategies to overcome oxidative damage or prooxidant chemoresistance [61, 62]. Even within a specific cancer type, the malignant cell populations are heterogeneous and intracellular oxidative levels may change as the disease progress [61]. Consequently, studying intra- and intertumor heterogeneous distribution of antioxidants levels may be an important factor to overcome tumor progression. Additionally, it is known that alterations in cellular redox metabolism play a crucial role in the activation or loss of tumor suppressor proteins activities such as breast cancer susceptibility gene breast cancer 1 (BRCA1) and phosphatase and tensin homolog deleted on chromosome 10
5. Conclusions

Enhancing the capacity of antioxidant in order to protect cells from redox-related changes or environmental toxins represents a persistent aim in the search for cytoprotective strategies against cancer. On the contrary, the strategy of depleting antioxidant is aimed at sensitizing cancer cells to chemotherapy, the so-called chemosensitization. In this context, it has been reported that antioxidant may be a determining factor for the sensitivity of some tumors to various chemotherapeutic agents. In particular, GSH and GSH enzyme-linked system are a relevant parameter for chemotherapeutic response, and it may be utilized as a useful biomarker for selecting tumors potentially responsive to chemotherapeutic regimens. The involvement of antioxidant in the carcinogenesis and in the drug resistance of tumor cell is clear, but further studies, aimed at understanding the antioxidant-driven molecular pathways and the biology of the tumor cells, are crucial to design new therapeutic strategies to fight cancer progression and overcome chemoresistance.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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