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Mini-review

Reactive oxygen species in redox cancer therapy

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ABSTRACT

The role of reactive oxygen species (ROS) in cancer cells has been intensively studied for the past two decades. Cancer cells mostly have higher basal ROS levels than their normal counterparts. The induction of ROS has been shown to be associated with cancer development, metastasis, progression, and survival. Various therapeutic approaches targeting intracellular ROS levels have yielded mixed results. As widely accepted dietary supplements, antioxidants demonstrate both ROS scavenging ability and anti-cancer characteristics. However, antioxidants may not always be safe to use since excessive intake of antioxidants could lead to serious health concerns. In this review, we have evaluated the production and scavenging systems of ROS in cells, as well as the beneficial and harmful roles of ROS in cancer cells. We also examine the effect of antioxidants in cancer treatment, the effect of combined treatment of antioxidants with traditional cancer therapies, and the side effects of excessive antioxidant intake.

Introduction

Reactive oxygen species (ROS) and associated oxidative stress have been historically considered harmful to the cell as they can damage cellular DNA, oxidize fatty acids in lipids and amino acids in proteins, and deactivate certain enzymes and their cofactors. The effects of these biological demolitions eventually lead to tissue destruction [1,2]. ROS have been associated with various diseases, including cardiovascular diseases [3], diabetes [4], and cancers [5]. In particular, elevated levels of ROS are implicated in cancer cells partly due to increased metabolic activity. To alleviate the detrimental effects of ROS, antioxidants are commonly considered to be beneficial to human health and are recommended as a dietary supplement intake [6]. Surprisingly, many clinical studies showed that the supplementation of antioxidants failed to impede the disease progression or extend the life expectancy of patients [7,8]. As a result, the biological roles of ROS have been re-examined. To date, it is still unclear whether ROS are part of the cause or the result of these diseases, and the biological roles of ROS in the body remain ambiguous. As "two-faced" molecules, ROS are involved in various complex signaling pathways and are critical to the fate of both healthy and diseased cells such as carcinomas. Specifically, disruption of ROS levels is one common approach in cancer therapies, as cancer cells are more vulnerable to ROS disruption than normal cells [9]. The survival rate of cancer cells can be reduced by either inducing or reducing intracellular ROS levels. Thus, antioxidants have also been often used along radiotherapy. However, the related therapeutic effects seem controversial [10]. Therefore, it is essential to discuss current progress regarding both positive and negative effects of ROS in modern cancer therapeutics, as well as the redox role in cancer development.

Oxidative stress

The continuous production and detoxification of cellular ROS lead to a tightly controlled and well-balanced redox status in normal cells. Oxidative stress, on the other hand, is caused by an imbalance

Abbreviations: Akt, protein kinase B; AMPK, 5′-adenosine monophosphate-activated protein kinase; ATM, ataxia telangiectasia-mutated; DR5, death receptor 5; EC, epicatechin; ECG, epicatechin-3-gallate; EGC, epigallocatechin; EGCG, epigallocatechin-3-gallate; EGF, epidermal growth factor; ETC, electron transport chain; GCL, glutamate cysteine ligase; GCLC, GCL catalytic subunit; GCLM, GCL modifier subunit; GSH, glutathione; GSR, glutathione-disulfide reductase; GSSG, glutathione disulfide; H_2O_2, hydrogen peroxide; HIF-1, hypoxia-inducible factor 1; IR, ionizing radiation; ISL, isoliquiritigenin; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinases; MTP, mitochondrial permeability transition; mTOR, mammalian target of rapamycin; NO, nitric oxide; NOS, nitric oxide synthase; Nrf2, nuclear factor erythroid 2-related factor 2; $O_2^{\bullet-}$, superoxide; $^{\bullet}OH$, hydroxyl radical; $ONOO^-$, peroxynitrite; PSO, psoralidin; ROS, reactive oxygen species; Se, selenium; SELECT, Selenium and Vitamin E Cancer Prevention Trial; SOD, superoxide dismutase; TLR, toll-like receptor; TRAF 6, tumor necrosis factor receptor-associated factor 6; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TrxR, thioredoxin reductase; TXN, thioredoxin; UVR, ultraviolet radiation.

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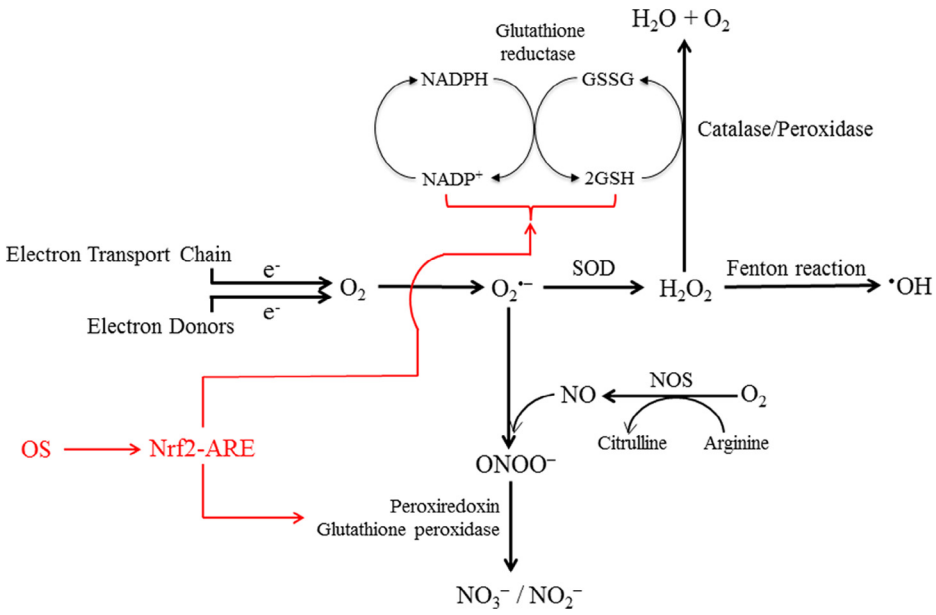

Fig. 1. This schematic demonstrates the major reactions and signaling pathways in ROS production and scavenging system. Abbreviations: antioxidant response element (ARE), electron (e^-), glutathione (GSH), glutathione disulfide (GSSG), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), nitric oxide (NO), nitric oxide synthase (NOS), nuclear factor erythroid 2-related factor 2 (Nrf2), oxidative stress (OS), peroxynitrite ($ONOO^-$), reactive oxygen species (ROS), superoxide ($O_2^{\bullet-}$), superoxide dismutase (SOD).

between ROS production and removal, which results in the accumulation of ROS in the cells. This could be attributed to the overproduction of ROS or the deterioration of the antioxidant system [2]. As mentioned previously, oxidative stress is believed to be associated with various diseases, yet the exact roles of ROS in these diseases have not been fully elucidated.

Production of ROS

The majority of ROS are produced in the electron transport chain (ETC) of mitochondria, mainly at complexes I and III [11]. In ETC, electrons from NADH are transferred to oxygen molecules (O_2) and eventually generate harmless water molecules. When only one electron is received, O_2 is reduced to superoxide ($O_2^{\bullet-}$), which can be further converted to hydrogen peroxide (H_2O_2) via superoxide dismutase (SOD) catalysis. Through a Fenton reaction, H_2O_2 can then be catalyzed to form a highly reactive ROS, hydroxyl radical ($^{\bullet}OH$) [12]. Moreover, $O_2^{\bullet-}$ reacts with nitric oxide ($NO^{\bullet}$) to generate peroxynitrite ($ONOO^-$) in a diffusion-controlled manner [13] (Fig. 1).

In addition to mitochondria, ROS are also formed in the cytoplasm by various enzymes [14]. Nitric oxide synthase (NOS) produces $NO^{\bullet}$ by facilitating the conversion of L-arginine to L-citrulline. The uncoupled NOS produces $O_2^{\bullet-}$ [15]. Electrons from NAD(P)H can transfer to O_2 and produce $O_2^{\bullet-}$ by NADPH oxidase, with the generation of $NAD(P)^+$ at the same time [16]. Other cellular enzymes, including xanthine oxidase, lipoxygenase, cyclooxygenases, and cytochrome p450 families, also participate in the generation of ROS during normal biological reactions [17] (Fig. 1).

Besides endogenous sources, environmental stresses, such as ultraviolet radiation (UVR), ionizing radiation (IR), and hypoxia, also induce cellular ROS production. In particular, UVB (a type of UVR) has been shown to activate oxidase and promote the uncoupling of NOS [18,19]. These enzymes then contribute to the production of $O_2^{\bullet-}$, $NO^{\bullet}$ and $ONOO^-$ [20]. In the case of IR, the water molecule is subjected to radiolysis, generating highly reactive molecules such as ionized water (H_2O^+), $^{\bullet}OH$, and H_2O_2 that will cause cellular DNA damage [21]. Additionally, IR upregulates the mitochondrial ETC function and results in more mitochondrial ROS production [22]. Hypoxia, the microenvironment experienced by many tumors, also activates various key regulators such as hypoxia-inducible factor 1 (HIF-1). The overexpressed HIF-1 leads to the generation of ROS, which in turn upregulates HIF-1, completing a positive feedback loop of ROS induction in the cells [11,23].

Antioxidant (ROS scavenging system)

The ROS scavenging system is mainly composed of antioxidant enzymes and non-enzymatic ROS scavengers. Common enzymes that are involved in the detoxification process of ROS are the following: SOD, which catalyzes the conversion from $O_2^{\bullet-}$ to O_2 or H_2O_2; catalase, which catalyzes the decomposition of H_2O_2 to H_2O and O_2; and family members of peroxidase, which help to reduce both H_2O_2

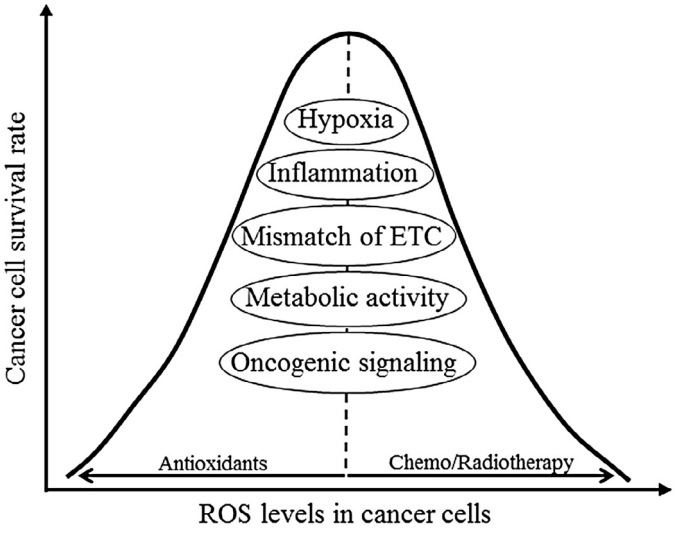

Fig. 2. This schematic demonstrates the critical roles of intracellular ROS levels in regulating the fate of cancer cells. Higher or lower ROS levels reduce the survival rate of cancer cells. In addition, antioxidants may diminish the effects of chemo/radiotherapy by lowering relative ROS production. Abbreviations: electron transport chain (ETC), reactive oxygen species (ROS).

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