

Potential Contributions of Antioxidants to Cancer Therapy: Immunomodulation and Radiosensitization

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Abstract

Antioxidants play important roles in the maintenance of cellular integrity and thus are critical in maintaining the homeostasis of the host immune system. A balance between the levels of pro-oxidants and antioxidants defines the cellular fate of genomic integrity via maintaining the redox status of the cells. An aberration in this balance modulates host immunity that affects normal cellular signaling pathways resulting in uncontrolled proliferation of cells leading to neocarcinogenesis. For decades, there have been scientific debates on the use of antioxidants for the treatment of human cancers. This review is focused on current updates on the implications of antioxidant use as adjuncts in cancer therapy with an emphasis on immunomodulation and radiosensitization.

Keywords

antioxidants, cancer therapy, immunosuppression, oxidized glycerophosphocholines, platelet-activating factor–receptor, immunomodulation, radiosensitization

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Introduction

The involvement of the reactive oxygen species (ROS) is well documented in various disease processes, including cancers.^{1–3} Under normal circumstances, the redox status of cells is maintained by a balance between ROS production and its sequestration by antioxidants.¹ While ROS is used as an innate mechanism of host immunity to fight against extracellular pathogens, including bacterial and viral infections, an exacerbated generation causes imbalance in cellular redox potential leading to alterations in signaling pathways and neocarcinogenesis.^{1–8} ROS release can be affected by several cellular compartments.^{9,10} As changes in the mitochondrial electron transport activity result in the production of ROS (mROS), heteroplasmic mutations in the mitochondrial DNA have been shown to increase the tumorigenicity of cancer cells via overproduction of mROS.^{8,11,12} Several cellular antioxidant systems, including superoxide dismutase and thioredoxin play crucial roles in counteracting the damaging effects of increased ROS.^{10,13} Cancer cells, particularly in the tumor microenvironment exhibit higher basal oxidative stress compared to normal cells and thus take advantage of the upregulated antioxidant system to circumvent ROS-mediated tumor cell damage.^{10,14,15}

Antioxidants and Immunity

The development of cancer has been linked to an inability of the host immune system to respond appropriately to tumor antigens, which leads to tumor immune evasion.^{16,17} The recognition and eradication of cancer cells by the immune system are categorized as elimination, equilibrium, and escape phases, referred to as the 3Es of immunoediting, which are governed by various factors.^{18–21} Briefly, in elimination phase, the host immune cells via the surveillance process recognize and try to eliminate nascent tumors.²¹ Whereas the equilibrium phase starts when a few tumor cells become resistant enough to sustain immune surveillance mechanisms and enter into the dormant stage, where equilibrium exists between tumor cell proliferation and immune cell-mediated apoptosis.^{21,22} An escape phase is established when tumor cells override their destruction by the immune system, an immunosuppressive environment is

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Table 1. Effect of Antioxidants on Host Antitumor Immunity: Evidences From Preclinical Studies.

Treatment	Experimental Model	Results	References
Curcumin	Swiss albino mice with Ehrlich ascites carcinoma cells	Restoration of tumor-induced depletion of host CD4+/CD8+ T cell proliferation, inhibition of thymocytes and splenocytes apoptosis, expansion of central memory and effector memory T cells and inhibition of suppressive activity of Tregs	27, 28
Resveratrol	BALB/c mice with 4T1 breast carcinoma cells	Inactivation of Stat3, prevention of tumor-evoked regulatory B cells (tBregs) generation and function and restricting the tBreg-induced conversion of FoxP3+ Tregs	34
Resveratrol	C57BL/6 and BALB/c mice with EG6 lymphoma and CT26 colon carcinoma cell lines	Suppression of tumor-derived Tregs	35
Fish oil and selenium yeast	BALB/cByJ mice with Line-1 and YAC-1 lymphoma cells	Decreased populations of immunosuppressive Tregs and myeloid-derived suppressor cells	36

maintained, which favors tumor cell proliferation, and the development of clinically detectable tumors is finally achieved.^{21,23} A direct link between antioxidants and modulation of cancer immunoediting has not been fully established. Nevertheless, curcumin has been shown to modulate immunoediting processes including resurrecting immune surveillance mechanisms to help eradicate cancer cells via (a) restoration of CD4+/CD8+ T cells, (b) suppression of T cell apoptosis, and (c) inhibition of immunosuppression through attenuation of immunosuppressive regulatory T cells (Tregs) (Table 1).²⁴⁻²⁸ Curcumin is a yellow-colored curcuminoid of turmeric of the family Zingiberaceae that is used as an herbal supplement, food flavoring and food coloring agent and is known to possess medicinal and anticarcinogenic properties that are attributed to its antioxidant and anti-inflammatory activities.²⁹⁻³¹ In addition, the antioxidant ascorbic acid (vitamin C) has been demonstrated to play an important role in stimulating the immune system via attenuating chronic inflammatory responses, the persistence of which is implicated in the etiology of various diseases, including cancer.³² Of note, chronic inflammation in tumors mediated via tumor infiltrating leucocytes (TIL) has been shown to induce immunosuppression and promote cancer growth.³³

Immunosuppression (ie, inhibition of the host immune system) via diverse environmental agents (such as ultraviolet radiation) acting on the skin is classically divided into local (localized to the site of application) and systemic immunosuppression.³⁷ Of importance, systemic immunosuppression has been implicated in human malignancies such as melanoma and glioblastoma.³⁸⁻⁴⁰ In most cancer models, tumor-dependent immune suppression has been recognized as one of the major events in promoting immune evasion of malignant cells from the host's antitumor immunity.⁴¹⁻⁴⁴ While tumor antigen-induced effector T-cells are required in inducing antitumor immunity, suppressor cells such as Tregs and

myeloid-derived suppressor cells (MDSCs) promote tumor escape mechanisms.⁴¹⁻⁴⁷ Importantly, immune checkpoint inhibitors such as cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been shown to mediate Tregs-induced immunosuppression and promote cancer growth. The blockade of these immune checkpoint inhibitors via anti-CTLA-4 and anti-PD-1 antibodies attenuates tumor growth as well as augments the effectiveness of cancer therapy approaches.⁴⁷⁻⁵⁰ Notably, Tregs and MDSCs have been shown to be associated with poor prognosis and cancer treatment failure, including immunotherapy and vaccination approaches.⁵¹⁻⁵³ Therefore, agents/anti-cancer drugs that target these immunosuppressive cell types are being explored in several preclinical and clinical cancer models and also in combination with known anti-cancer drugs against various malignancies.⁵⁴⁻⁵⁷ With regard to antioxidant use in attenuating the enhanced tumor growth mediated by these immunosuppressive cells, studies by Lee-Chang et al³⁴ have shown that administration of resveratrol, a dietary polyphenol compound possessing antioxidant properties at low doses that are nontoxic to immune cells, inhibits lung metastasis of breast cancer tumor. This resveratrol-induced effect was mediated via Stat3 inactivation, resulting in an inhibition of the generation and function of tumor-evoked regulatory B cells (tBregs) and their conversion into Tregs. In support of these findings, studies by Yang et al³⁵ have demonstrated that suppression of tumor-derived Tregs mediates resveratrol-induced inhibition of syngeneic murine EG7 lymphoma and CT26 colon carcinoma tumors in C57BL/6 and BALB/c mice models.³⁵ Of importance, resveratrol can exert both antioxidant and pro-oxidant properties depending on its concentration and cell types used.⁵⁸ Along similar lines, Wang et al³⁶ have demonstrated that a combination of fish oil and selenium that possesses anti-inflammatory and antioxidant activities exerted synergistic effects in suppressing lung tumor growth mediated via decreasing the

population of splenic Tregs and MDSCs and thus augmented host anti-tumor immunity against lung carcinoma.

Exposure to pro-oxidative stressors generating ROS, including ultraviolet B (UVB) radiation and cigarette smoke (CS), is associated with the modulation of host immunity. Studies including ours have demonstrated the beneficial effects of antioxidant administration, including vitamin C and *N*-acetyl cysteine (NAC) in attenuating the systemic immunosuppressive effects of various environmental pro-oxidative agents, including UVB and CS in animal models.⁵⁹⁻⁶⁵ Of significance, UVB and CS generate a class of oxidized lipid mediators nonenzymatically via free radical mediated attack on membrane phospholipid glycerophosphocholines (ox-GPCs).⁵⁹⁻⁶⁵ In contrast, enzymatic synthesis of platelet-activating factor (PAF, 1-hexadecyl-2-acetyl-glycerophosphocholine) is a tightly regulated process, which requires cytoplasmic phospholipase A₂ (cPLA₂) that acts on 1-alkyl glycerophosphocholines (GPC) with *sn*-2 long-chained unsaturated fatty acids (eg, arachidonate) forming the lyso species which then is acetylated, forming PAF.^{66,67} These ox-GPCs possess PAF and PAF-like agonist activities, which bind to and activate a 7-transmembrane G-protein coupled receptor, the PAF-receptor (PAF-R) which is expressed on various cell types (immune and nonimmune) including keratinocytes and tumor cells.⁵⁹⁻⁶⁸ Our group uses 2 functional assays to quantify total PAF-agonists by very specific interleukin 8 (IL-8) protein or Ca²⁺ mobilization using stably PAF-R expressing (KBP) and deficient (KBM) cells generated retrovirally from human epidermal KB cells.^{59-62,65,69-71} The activity of Ox-GPCs/PAF is regulated by PAF-acetyl hydrolases (PAF-AH; PLA2G7).⁶⁶⁻⁶⁸ Of 3 types, PAF-AHI is the major plasma isoform. PAF-R activation mediates various biological activities including early pro-inflammatory and delayed systemic immunosuppressive effects.⁵⁹⁻⁶⁴ Our research group and others have shown that ox-GPCs/PAF-R agonists mediate UVB- and CS-induced systemic immunosuppression in a PAF-R dependent manner which is measured by inhibition of contact hypersensitivity (CHS) or delayed type hypersensitivity (DTH) responses to an eliciting allergen, dinitrofluorobenzene (DNFB) or an antigen, *Candida albicans*.⁵⁹⁻⁶⁴ In using this methodology, for example, to measure UVB-mediated systemic immunosuppression, the shaved dorsal back skin of mice were exposed to UVB. A group of mice injected intraperitoneally with either PBS or the PAF-R agonist, CPAF served as negative and positive controls. Five days later, a 2x2 cm area of the back skin (approximately 2.5 cm distant from the UVB-radiated site) was sensitized with 0.5% DNFB topically. After 9 days, postelicitation changes in CHS were assessed by measuring changes in ear thickness. With similar methodology, the local immunosuppressive effect of UVB is assessed when dorsal skin of mice is sensitized with DNFB onto the UVB-exposed area (a model of local immunosuppression) and usually required lower UVB doses. Using this

methodology we have demonstrated that PAF-R does not mediate UVB-induced local immunosuppressive effects,⁶⁵ despite its effect in mediating systemic immunosuppression. This PAF-R-dependent systemic immunosuppression is mediated via upregulation of COX-2 enzyme and COX-2-generated prostanoids, immunosuppressive cytokine interleukin 10 (IL-10) and the Tregs cell type, in a process blocked by antioxidants.⁵⁹⁻⁶⁴ As both environmental and therapeutic pro-oxidative stressors generate ROS and thus ox-GPCs/PAF-R agonists, we have shown that supplementation of vitamin C and NAC in drinking water prophylactically suppressed generation of ox-GPCs/PAF-R agonists mediated by UVB, chemotherapy, and radiation therapy—as well as diminishing the augmentation of tumor growth induced by systemic immunosuppression.⁶⁹⁻⁷¹ Several standard chemotherapeutic agents, including dacarbazine and melphalan generate PAF-R agonists from both murine and human melanoma cells in vitro and intratumorally treated melanoma tumor xenografts in vivo.⁷⁰ Using a dual tumor model, we demonstrated that intratumoral melphalan (MELP) chemotherapy (of one tumor) augments the growth of secondary (untreated) B16F10 melanoma tumor in a PAF-R dependent manner.⁷⁰ Systemic antioxidants, COX-2 inhibitors or depleting Treg Abs attenuated this MELP-mediated enhanced growth of secondary tumors in WT mice,⁷⁰ indicating the role of oxidatively generated PAF-R agonists and downstream COX-2 and Tregs in modulating MELP efficacy. Nevertheless, antioxidant use postchemotherapy or to augment cancer therapy effectiveness in pre-clinical cancer models with regard to immunosuppression requires further investigation.

Antioxidants in Cancer Therapy

Despite recent advances in local and systemic treatment modalities, chemotherapy, radiation therapy and immunotherapy are widely considered either alone or in combinations for a variety of cancers. In chemotherapy, cancer cells are targeted by chemically modified agents/natural compounds with cytotoxic properties; radiation therapy uses high-energy particles/waves, including x-rays and gamma rays, to kill tumor cells; and immunotherapy treatments are designed to stimulate the host's own immune system to attack cancer cells. One of the consequences of chemotherapy and radiation therapy is the generation of ROS which via its direct and indirect effects on tumor cells, induces DNA damage and/or affects DNA replication machinery, leading to aberrations in several cellular signaling pathways resulting in chemotherapy- or radiation therapy-induced cell death.⁷²⁻⁷⁴ Most of these therapies are not considered a good option as a single agent to treat advanced-stage/metastatic cancers, in part due to the development of therapy-induced innate and/or acquired tumor resistance or local/systemic toxicities leading to either reduced response, nonresponsiveness or tumor relapse after

an initial antitumor response.^{75,76} Therefore, potentially new therapeutic approaches with agents that exhibit anticancer properties and can potentiate chemotherapy- or radiation therapy-mediated antitumor responses are required for inducing optimal and long-term benefits in cancer patients.

Several nutritional cancer chemopreventive compounds having antioxidant properties have been documented to potentiate radiation therapy-induced cytotoxic effects on cancer cells while reducing its toxicity on normal surrounding tissues.⁷⁷⁻⁸⁶ In this regard, multiple studies by Raffoul et al⁷⁸ have shown that phytochemical soy isoflavones (genistein, daidzein, and glycitein), which exhibit anticarcinogenic properties in part via their antioxidant activities, could be used as potent radiosensitizers to enhance the efficacy of radiotherapy-mediated suppression of the growth and metastatic ability of cancers, including prostate cancer.⁷⁸⁻⁸⁰ A study comparing the effects of the soy isoflavone component genistein on prostate cancer demonstrated that both soy and genistein inhibited the growth of in vitro human PC-3 prostate cancer cells and in vivo orthotopic PC-3 tumors and that these effects were enhanced when soy or genistein was combined with radiotherapy.⁷⁹ Mechanistically, soy isoflavones attenuated the radiation-induced increase in expression of apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) and activation of NF- κ B and its DNA-binding activity, resulting in potentiating radiotherapy-mediated effects and their use as radiosensitizers.⁷⁹ In addition, soy isoflavones have been shown to augment radiation-induced suppression of in vitro growth of human A549 non-small cell lung cancer cells via inducing increased DNA damage, inhibition of APE1/Ref-1 mediated DNA repair and decreased expression of the transcription factors NF- κ B and HIF-1 α .⁸² Importantly, agents possessing proteotoxic stress activities have been shown to enhance radiosensitization. In this regard, Pruitt et al⁸³ have demonstrated that dietary polyphenols known as hydroxychalcones augmented radiation-mediated death of human colorectal adenocarcinoma HT-29 and pancreatic cancer Panc 1 cells. These effects were mediated via activation of the heat shock factor 1 (Hsf1) in a process blocked by prophylactic treatment with α -naphthoflavone (ANF), a specific inhibitor of cytochrome P450 1A2 (CYP1A2).⁸³ Along similar lines, resveratrol and piperine, which possess properties including antitumor activities, have been shown to augment ionizing radiation (IR)-induced apoptosis and loss of mitochondrial membrane potential in murine colon carcinoma CT26 and melanoma B16F10 cells via enhancing IR-induced ROS generation.⁸⁴ Moreover, pentoxifylline (PTX), a methylxanthine that possesses antioxidant properties is known to improve tumor tissue oxygenation in murine hypoxic tumors as well as inhibiting post radiation-induced normal tissue injury in mice.⁸⁵⁻⁸⁸ Importantly, PTX has been shown to enhance radiation-mediated effects in human breast MCF-7 and colon HT-29 carcinoma cells in

vitro and murine mammary adenocarcinoma SCK tumors in A/J mice in-vivo.⁸⁵⁻⁸⁸ In vitro studies, PTX treatment has been shown to enhance radiotherapy-mediated effects in a dose and time dependent manner in post-irradiated cells, and did not change the cellular response to radiation in pre-irradiated cells.⁸⁶

Several chemotherapeutic agents used for the treatment of human malignancies generate ROS as one of the potent mechanisms to eradicate tumor cells via targeting multiple oncogenic signaling pathways. Hence, targeting ROS by antioxidants not surprisingly has yielded mixed results in the therapeutic efficacy of chemotherapy.⁸⁹⁻⁹¹ Importantly, in a systematic review, Block et al^{92,93} have summarized the impact of antioxidant supplementation on the efficacy and toxicity of chemotherapeutic agents from several randomized controlled trials (RCTs). Antioxidants such as glutathione, melatonin, vitamin A and E, NAC, selenium, L-carnitine, Co-Q10, ellagic acid, an antioxidant mixture such as vitamin C and E with beta-carotene or selenium supplementation were evaluated on the efficacy of chemotherapeutic regimens, including oxaliplatin and cisplatin in combinations with agents such as etoposide, gemcitabine for several malignancies including breast, lung and gastric cancers.⁹⁰ Survival of patients and tumor response were the primary outcomes of these trials.⁹⁰ While a statistically significant improved survival rate either at 1 year or 5 years was associated with melatonin supplementation, vitamin A exerted mixed responses on therapy outcomes and no significant differences in the tumor response or survival were reported with other antioxidants.⁹⁰ Of significance, 24 RCTs reported significantly decreased toxicities with concurrent supplementation of antioxidants (mentioned above) with chemotherapy in cancer patients compared to patients who were not on systemic antioxidants (controls).⁹¹ On the other hand, 9 RCTs reported no differences in the toxicities by antioxidants supplementation and 1 RCT with vitamin A reported increased toxicity.⁹¹ Along similar lines, a systematic review on RCTs by Yasueda et al⁹⁴ summarized that it is difficult to determine whether antioxidant supplements affect treatment outcomes or ameliorate adverse effects induced by chemotherapy and radiotherapy. The authors concluded that harm caused by antioxidant supplementation remained unclear for patients during cancer therapy, except for smokers undergoing radiotherapy.⁹⁴ As cancer patients experience therapy-induced adverse side effects, including weight loss due to low nutritional intake and/or loss of appetite, individualized counsel for the use of antioxidants or supplements with antioxidant properties during treatment is important to circumvent its detrimental effects and/or therapy outcome.

Conclusion

While the safety and benefits of antioxidants use during cancer treatment are limited, their indispensable role in the maintenance of immune system homeostasis cannot be

overruled. A large percentage of cancer patients undergoing active treatments uses antioxidants and not all antioxidants are likely to be beneficial; as well, their mode of action on cellular systems and interaction with anticancer drugs remained largely unexplored. Therefore, further preclinical and clinical studies are needed to establish the clinical implications of antioxidant doses and timings based on treatment regimens, disease stage, and especially immune suppression status.

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