Antioxidants in Translational Medicine

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FORUM REVIEW ARTICLE

Antioxidants in Translational Medicine

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Abstract

Significance: It is generally accepted that reactive oxygen species (ROS) scavenging molecules or antioxidants exert health-promoting effects and thus their consumption as food additives and nutraceuticals has been greatly encouraged. Antioxidants may be beneficial in situations of subclinical deficiency and increased demand or acutely upon high-dose infusion. However, to date, there is little clinical evidence for the long-term benefit of most antioxidants. Alarmingly, recent evidence points even to health risks, in particular for supplements of lipophilic antioxidants. ***Recent Advances:*** The biological impact of ROS depends not only on their quantities but also on their chemical nature, (sub)cellular and tissue location, and the rates of their formation and degradation. Moreover, ROS serve important physiological functions; thus, inappropriate removal of ROS may cause paradoxical reductive stress and thereby induce or promote disease. ***Critical Issues:*** Any recommendation on antioxidants must be based on solid clinical evidence and patient-relevant outcomes rather than surrogate parameters. ***Future Directions:*** Such evidence-based use may include site-directed application, time-limited high dosing, (functional) pharmacological repair of oxidized biomolecules, and triggers of endogenous antioxidant response systems. Ideally, these approaches need guidance by patient stratification through predictive biomarkers and possibly imaging modalities. *Antioxid. Redox Signal.* 23, 1130–1143.

Introduction

Since the 1970s, oxidative stress has been evoked as a contributor to pathogenesis and thousands of studies have reported protective or therapeutic benefits of antioxidants in cellular and animal models of cardiovascular (43), neurodegenerative (62), and inflammatory diseases (75) and cancer (110) diseases. As a result, antioxidant supplements have been promoted as nutraceuticals and antioxidant vitamins, often with little or no clinical control or evidence.

Failures and risks of antioxidants

However, with the exception of a few studies (50, 53, 67), antioxidants have almost always failed to show a significant effect in long-term clinical trials performed according to the criteria of evidence-based medicine (132). For example, the spin-trapping synthetic antioxidant NXY-059, developed for acute treatment of ischemia injury due to stroke, represents one of the most prominent and costly failures of a synthetic antioxidant ever clinically developed (135). Another example is the recent failure of the 2CARE study on the use of

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coenzyme Q10 in the largest ever therapeutic trial for Huntington's disease (61b).

In some recent meta-analyses, a beneficial effect of antioxidants was claimed, such as for vitamin C in breast cancer (47), atrial fibrillation (2), stroke (25), or endothelial function (5). However, a more definitive proof of antioxidant benefit would have been required to measure plasma levels of the administered compounds. The latter was also a major limitation in several large clinical trials, for example, the Heart Outcomes Prevention Evaluation (HOPE) (137, 158) and the HOPE-The Ongoing Outcomes (17). Even worse than no effect, chronic use of multivitamins without clinical control, especially lipid-soluble antioxidants at dosages above the upper safety limit, may be associated with increased health risks (Table 1) (13).

In sedentary rats, vitamin E administration reduced liver oxidative damage, while in rats submitted to chronic exercise, vitamin E decreased antioxidant levels (148). It remains controversial whether chronic intake of high concentrations of certain antioxidants has a harmful effect on performance and whether this might be due to redox cycling reactions that could even convert an antioxidant into a pro-oxidant (18, 116, 125). Taken together, these observations indicate that to identify efficient redox-based therapeutic strategies, there is first a need to reevaluate the physiological and pathological relevance of reactive oxygen species (ROS), and then to determine whether an antioxidant approach is feasible and in which situations.

Another example of the failure of antioxidant therapy is provided in pre-eclampsia. Some studies have reported a modest increase in oxidative stress biomarker, F2-isoprostane, at late stages of pregnancy (112) as well as low levels of gamma-tocopherol may be considered as a risk factor for pre-eclampsia (63). However, concomitant supplementation with vitamin C and vitamin E did not prevent pre-eclampsia in women at risk and, even worse, this treatment increased the rate of births with low weight (121).

Absorption, distribution, metabolism, and excretion of specific antioxidants are essential aspects of antioxidant therapy that have not been analyzed in detail for many compounds, especially for nutraceuticals. Yet, the pharmacokinetic (bioavailability and frequency of administration) and pharmacodynamic (therapeutic index and onset of action) properties of specific antioxidants are critical to assess their clinical usefulness (11). This is best exemplified with compounds that need to cross the blood–brain barrier (73).

Redefining oxidative stress

The term, ROS, groups a number of oxygen-containing molecules with different chemical reactivity. ROS include not only $O_2^{-\bullet}$, hydroxyl radicals, alkoxyl and peroxyl radicals, $^{\bullet}NO$, and nitrogen dioxide radicals but also nonradical species such as hydrogen peroxide (H_2O_2), hypochlorite, peroxynitrite, singlet oxygen, lipid peroxides, and others. At the enzymatic level, the discovery of superoxide dismutases (SOD), catalase, peroxiredoxins, sulfiredoxins, and glutathione peroxidases implied that the formation of at least some forms of ROS, for example, $O_2^{-\bullet}$, can be harmful if not properly controlled (24, 90, 140).

At the chemical level, when talking about ROS and ROS scavengers, it is crucial to know what kinds of molecules are involved. For instance, in the case of ascorbate, this antioxidant avidly reacts with alkyl, peroxyl, and alpha-tocopheroxyl radicals, modestly with superoxide, and poorly with H_2O_2. While ascorbate also reacts very rapidly with hydroxyl radicals, this unlikely contributes to its antioxidant

Table 1. Meta-Analyses and Reviews of Chronic Oral Vitamin and Antioxidant Substitution

Study type	*Antioxidants assessed*	*Objectives and endpoint*	*Conclusions*
Meta-analysis (150)	β-Carotene and vitamin E	Effects on CVD-related and unrelated mortality and morbidity	β-Carotene possibly harmful; vitamin E no effect
Meta-analysis (14)	β-Carotene, vitamins A, C, E, and selenium, alone and mixed	Incidence of cancer and dose–response effect on mortality	High-dose vitamin E may increase mortality; selenium may be beneficial in the prevention of cancer; other antioxidants no effect
Review (81)	β-Carotene, vitamin E, and antioxidant cocktail	Primary and secondary prevention of CVD and progression of intima-to-media thickening	Data do not justify supplementing antioxidants beyond the current dietary guidelines
Meta-analysis (102)	Vitamin E alone and in combination	Dose–response effect on all-cause mortality rates	High-dose vitamin E may increase all-cause mortality and should be avoided.
Meta-analysis (133)	Vitamin E	All relevant CVD-related endpoints and lipid levels	Vitamin E does not affect CVD-related outcomes.
Meta-analysis (36)	Vitamin E alone and in combination	Odds ratio of relevant CVD-related endpoints	Vitamin E no effect
Meta-analysis (13)	β-Carotene, vitamins A, C, E, and selenium, alone and in combination	All-cause mortality with regard to other factors such as dose and type of supplement	β-Carotene and vitamins A and E may increase mortality
Decision tree and Markov chain model (33)	Vitamin E alone and in combination	Event rates and quality-adjusted life year	Nonselective application of high-dose vitamin E does more harm than good

CVD, cardiovascular disease.

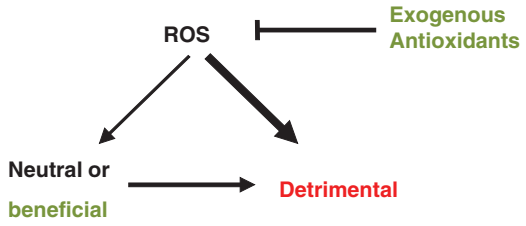

FIG. 1. Classical view on oxidative stress and antioxidants. Initially reactive oxygen species (ROS) were seen as a metabolic by-product that in low concentrations is neutral or beneficial (having signaling effects), but in higher concentrations can lead to a cellular, tissue, or even whole body redox imbalance with detrimental consequences. Hence, it was seen feasible to initiate systemic treatment with ROS scavengers as antioxidants to reverse this imbalance by reducing ROS levels. Such exogenous antioxidants were not expected to have any possible side effects. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

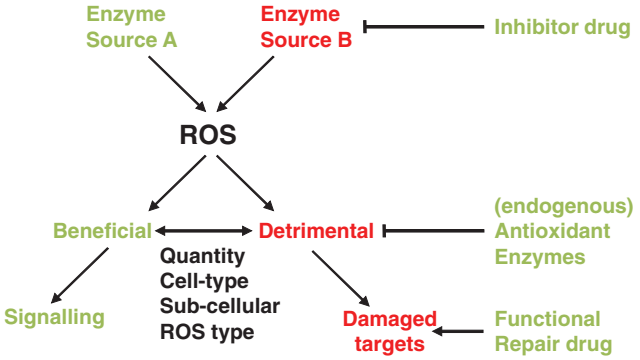

FIG. 2. Refined scheme and major changes in our understanding of oxidative stress and possible interventions. ROS are now viewed not necessarily as disease-triggering molecules but also as essential signaling messengers. The distinction between beneficial and detrimental effects of ROS cannot be defined by overall cell, tissue, or whole body quantity of ROS formation. Instead, these differences may be due to different sources of ROS in different cellular and subcellular compartments (physiological and nonphysiological), the type of ROS being formed (*e.g.,* superoxide *vs.* hydrogen peroxide). In light of the many negative results with broad systemic antioxidants, new therapeutic approaches may include more targeted or specific antioxidants, limiting antioxidants only to situations with acute and extremely high ROS levels, or indirect antioxidant mechanisms by upregulating endogenous antioxidant defense systems. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

activity because hydroxyl radicals are so reactive that they react with essentially all molecules at diffusion-controlled rates so that ascorbate will always be outcompeted.

Originally, the term oxidative stress was primarily defined by quantitative deviation from a supposedly neutral steady-state level of ROS (136, 140). Quantitative deviation means a state where either increased formation of ROS or diminished cellular antioxidant defense leads to disequilibrium and a shift in the cellular redox balance (Fig. 1). However, we now know that for ROS, as for many other messengers, cellular levels are less relevant compared with subcellular concentrations (20, 68).

Quantity, that is, deviation from an overall equilibrium, on its own cannot explain or define oxidative stress. In fact, at least in many experimental models, only very moderate overall increases in ROS levels are observed, yet correlating with appreciable dysfunction and accumulation of relevant biomarkers (154). Therefore, in addition to quantitative accumulation of ROS, the oxidative stress concept needs to integrate other features of ROS such as their subcellular or tissue location, chemical nature (*e.g.,* $O_2^{-\bullet}$, H_2O_2, $ONOO^-$), kinetics of formation and degradation, and time of exposure (Fig. 2) (76). Examples include the expression of NOX1 in hypertension, causing only a small increase in ROS (154), but *via* its caveolar localization, its product $O_2^{-\bullet}$ interferes with $^\bullet NO$ formation and its vasodilator function (88); conversely, H_2O_2 induces endothelial nitric oxide synthase (eNOS) and is a vasodilator (34, 100).

Physiological functions of ROS

Another potential problem of antioxidants is the many physiological functions of ROS. The discovery of NOX isozymes, the only known enzyme family with the sole purpose of producing ROS, indicated that at least certain ROS are physiologically essential. For a long time, and still for newcomers to the field, it was considered that the increased formation of ROS equates to oxidative stress and represents a biochemical accident that can be prevented by systemic antioxidant treatment (mostly cell culture or animal-based studies using high doses of the drug). This misconception is based on the wrong assumption that ROS fulfill no physiological function. The first description was the role of NOX2 (then termed gp91phox) in immunocyte oxidative burst.

Other NOX isoforms have different physiological roles in nonphagocytic cells, for example, in hearing (111), thyroid hormone synthesis (32) and angiogenesis, and the constriction of the ductus arteriosus (72). Furthermore, ROS play important roles in normal cellular function, including differentiation, proliferation, aging, and repair processes (124). Nitric oxide/nitrogen monoxide ($^\bullet NO$) and H_2O_2 seem to act primarily as messenger molecules, for example, they essentially contribute to vasodilation, proliferation (103), and promote or counteract programmed and spontaneous cell death (apoptosis and necrosis) (12, 147).

In working muscles, ROS are generated in the microcirculation, sarcolemma, and mitochondria (64) as part of a beneficial physiological response. Depending on mode, intensity, and duration of the exercise, antioxidants thus affect exercise capacity and adaptation processes (Fig. 3). For example, antioxidants, such as vitamins C and E, appear to blunt exercise-induced mitochondrial biogenesis (116); even anaerobic exercise, for example, strength training, can be affected with respect to muscle strength and hypertrophy (94, 117). Other observations indicate that vitamin C supplementation decreases oxidative stress and might increase exercise performance only in those subjects with low initial concentration of vitamin C (114).

Both the redefinition of oxidative stress (from a global redox disequilibrium to very subtle, even subcellular changes) and the many physiological functions of the same ROS that also cause disease may explain why systemic and chronically applied antioxidants may not necessarily have beneficial effects or even cause reductive stress or harm (9).

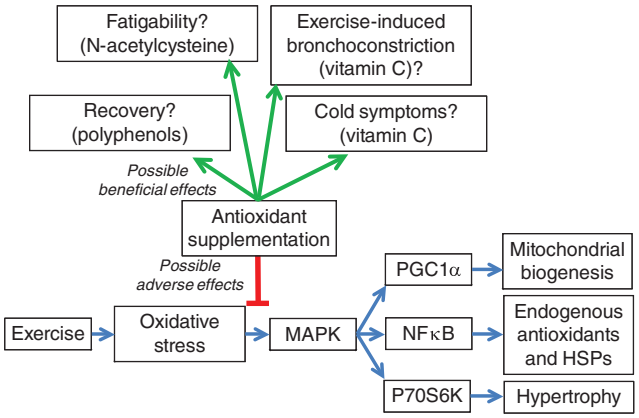

FIG. 3. Simplified scheme of antioxidant supplementation outcomes in exercising individuals. Possible adverse effects are linked to blunted cell signaling and adaptation to exercise by reducing oxidative stress. The adaptations will depend on the exercise mode (endurance *vs.* strength), but MAPKs may be important signaling proteins (65). The possible positive effects could not only be linked to the exercised muscles (reduced fatigability and improved recovery) but also the upper respiratory system by alleviating common cold symptoms and exercise-induced bronchoconstriction (10, 51, 52, 101). HSP, heat shock proteins (*e.g.,* HSP70); JNK, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinases (p38, ERK1/2 and JNK); NFκB, nuclear factor kappa B (transcriptions factor); PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha. Endogenous antioxidants include superoxide dismutase, catalase, and glutathione peroxidase. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

For example, ROS formed during the oxidative burst of phagocytic cells protect against infection and tumor cells, which imposes the risk of any chronically applied antioxidant (71, 118, 129). On the other hand, experimental data support the hypothesis that vitamin C affects epigenetic reprogramming toward less invasiveness of tumor cells (44, 149, 156).

Paradoxes between in vitro versus in vivo *and animal* versus *human studies*

One potentially large problem in the field of ROS may be the use of *in vitro* models to observe cytoprotective effects of antioxidants. Standard cell culture, isolated organs, and cell-free models represent artifact-prone conditions due to a very high partial oxygen pressure of about 0.2 m*M* (79). In addition, the frequently published exposure of cells to a bolus of high micromolar concentrations of an oxidant is nonphysiological, even if this may be reached in some subcellular compartments or intercellular spaces. It likely impairs cellular antioxidant defenses in a manner that is hardly ever seen *in vivo* (46).

Yet, it remains puzzling why so many *in vivo* animal studies that have shown beneficial effects of antioxidants were later not translatable into the clinic because they failed to show benefit or in some studies, HOPE (95, 157), HOPE-TOO (89), a prospective study with vitamin C in postmenopausal women with diabetes mellitus (82), and a prospective cohort study conducted among 83,639 healthy male US physicians (107), worsened outcome (Table 1). However, these and other studies often do not monitor plasma concentrations of the supplemented antioxidant. Measurement of drug levels in tissues where the disease process is to be modified by the drug is not always practical (*e.g.,* the central nervous system, heart) and target engagement biomarkers may be more helpful. Nevertheless, even in these cases, plasma levels of the drug serve important purposes, such as determination of drug safety and effective drug range.

Thus, it is possible that the lack of response had pharmacokinetic rather than pharmacodynamic reasons. In the European Prospective Investigation into Cancer (EPIC)-Norfolk study, vitamin C concentrations correlated with lower risk of all-cause mortality (77) and, in a meta-analysis of prospective studies, with a lower risk of stroke (25).

According to meta-analyses, long-term, high-dose N-acetylcysteine (NAC) treatment may improve the clinical complications of patients with chronic obstructive pulmonary disease (134) and the prophylactic use of NAC could reduce the incidence of postoperative atrial fibrillation and all-cause mortality in adult patients undergoing cardiac surgery (87). However, apart from a possible publication bias, such non-interventional observational studies and correlations cannot establish cause–effect relationships.

Other reasons for the failure of chronic oral antioxidant therapy may include the slow reaction constants between superoxide and vitamins C and E (3.3×10^5 and 4.9×10^3 $m^{-1}s^{-1}$, respectively, compared with 1.9×10^{10} mol^{-1} s^{-1} for the reaction constant between $^{\bullet}NO$ and superoxide) (141). Moreover, the inclusion criteria for patients can never be as restrictive as in preclinical studies, and in some cases, the disease may be at different stages of progression or clinical manifestation. In addition, as indicated before, in most cases, chronic, oral vitamin treatment has not been monitored consistently to provide plasma level concentrations or changes in target engagement biomarkers.

The differences between preclinical stages and clinical settings are also affected by differences in the antioxidant drug's mechanism of action and especially due to pharmacokinetic and pharmacodynamic constraints (11). This is best exemplified with compounds that need to cross the blood–brain barrier (73).

Finally, it is interesting to note that basic research is biased by the lack of publications with negative results while most outcomes of clinical trials are reported. Therefore, it is possible that this paradox is due, in part, to an underrepresentation of the real outcomes in preclinical studies.

Nonredox mechanisms of antioxidants

In other cases, the action of compounds with antioxidant activity may actually involve nonredox mechanisms, such as intercalation of DNA and/or inhibition of topoisomerase, DNA polymerase, and ribonucleotide reductase (40). Flavonoids and other phytochemicals can bind to functionally diverse cellular targets and this may modulate the activity of a large number of downstream genes (4).

Ongoing Development of Direct Antioxidants

Figure 4 depicts some conceptual strategies used to block the imbalanced production of ROS. Despite the failures and concerns with the use of antioxidant therapy, there are still several clinical studies and developments ongoing to translate the direct antioxidant principle into the clinic. Most of the antioxidant therapies so far utilized compounds that donate either one or two electrons, which require high

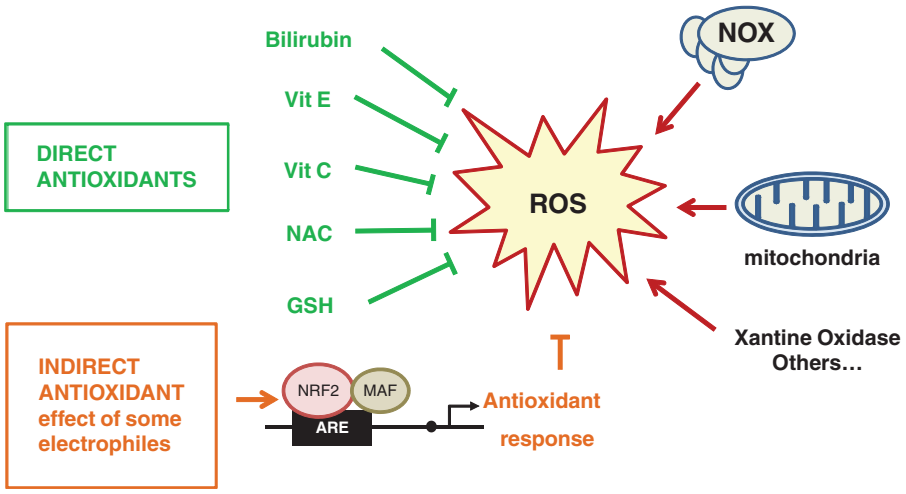

FIG. 4. Conceptual approach to the use of small molecules as direct and indirect antioxidants. The main sources of ROS production include NOX, mitochondria, xanthine oxidase, and other enzymes. Direct antioxidants (*green*) react with ROS and, if properly handled, may decrease oxidative stress. Indirect antioxidants (*orange*) activate cellular antioxidant defenses, such as NRF2-mediated gene transcription, and provide a supplemental enzymatic armamentarium to maintain redox homeostasis. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

concentrations and impose the risk of converting the antioxidant into a pro-oxidant. To allow for lower doses, one alternative approach is to use compounds that are recycled by cellular reductases or act catalytically (90).

Recycling antioxidants

Ascorbate typically reacts with free radicals, producing an ascorbyl radical intermediate that may be reduced back or undergo further oxidation to dehydroascorbic acid, for which specific reductases exist (86). Other recycling antioxidants include low-molecular-weight thiols (*e.g.,* glutathione and acetylcysteine), thioethers (*e.g.,* methionine), and many more. In the case of vitamin E (α-tocopherol, in which case recycling depends on nonenzymatic reactions), BO-653 was developed as a synthetic, improved vitamin E-like molecule for the treatment of cardiovascular disease (intimal hyperplasia), but it failed in clinical trials (28). Other examples are the above-mentioned synthetic antioxidant NXY-059 that failed to improve outcomes in stroke patients (135) or coenzyme Q10, which failed to improve prognosis of patients with Huntington's disease (61b).

The glutathione peroxidase mimetic, ebselen (2-phenyl-1,2-benzoisoselenazol-3(2H)-one), was once considered a promising synthetic antioxidant since it reacts rapidly with peroxides (106, 153) and peroxynitrite (98), preventing lipid peroxidation and oxidative damage of other biomolecules. However, ebselen failed due to severe liver toxicity and inhibition of thiol-dependent enzymes (29). Compounds with a metal center such as SOD or catalase can in principle detoxify $O_2^{-\bullet}$ and H_2O_2 in a catalytic manner.

Trace elements such as zinc and selenium may augment antioxidant enzyme activity, but it will be difficult to ascribe their beneficial properties to modulating oxidative stress and not to other effects related to their function as cofactors of nonredox proteins. Metal porphyrins (FeTMPyP, FeTMPS, MnTBAP) were not only developed as SOD mimetics (61, 115) but unfortunately also showed pro-oxidative activities in biological systems and, so far, have not reached the stage of clinical application.

A possible alternative includes mitochondria-targeted SOD mimetics, for example, Mn(III) 5,10,15,20-tetrakis(N-methylpyridinium-2-yl)porphyrin (MnTM-2-PyP(5+)) (7, 8), or the so-called next-generation SOD mimetics. This compound class includes Mn-pentaazamacrocycles such as GC4403 (6, 128). This and other members of the Mn-pentaazamacrocyclic ligand class of SOD mimetics function by a one-electron redox cycle, with oxidation of Mn(II) being the rate-determining step (6).

In animal models of oxidative stress caused by total body irradiation, GC4403 increased survival, decreased intestinal apoptosis, protected lymphoid and hematopoietic tissues (143), and reduced the incidence and severity of radiation-induced mucositis (108). A related compound, GC4419, is currently in Phase IIa testing (NCT01921426) in patients undergoing standard chemoradiation treatment of head and neck cancer, a setting in which up to 80% of patients develop severe oral mucositis.

Mitochondria-targeted antioxidants

The direct and specific targeting of mitochondrial ROS formation by mitochondria-targeted antioxidants is another strategy still pursued to date. This will decrease mitochondrial ROS and prevent oxidative damage of important mitochondrial structures from ROS produced by extramitochondrial sources (*e.g.,* mitochondrial DNA is not well protected since efficient DNA repair systems do not exist in the matrix).

One of the first examples for this class of compounds was mitoquinone (1, 80), a quinone coupled to triphenylphosphonium, leading to significant accumulation in mitochondria. mitoTEMPO is another promising candidate for targeting mitochondrial ROS as it prevents adverse effects of angiotensin-II in experimental hypertension (30). A drawback of this strategy could be that these compounds require viable mitochondria with a certain membrane potential for uptake, which could limit their accumulation and accordingly antioxidant potency, especially in dysfunctional ROS-producing mitochondria. Several candidates of these mitochondria-targeted antioxidants are currently in late-phase clinical trials (109, 138).

Pharmacokinetic targeting

Another clinical approach to overcome the limitations or lack of evidence of chronic oral antioxidant therapy is the short-term infusion of antioxidants such as vitamin C. Positive reports include the reduction of histamine levels in allergy (45), enhanced hearing recovery in idiopathic sudden hearing

loss (74), anti-inflammation improved recovery and lower rate of complication in pancreatitis (35), reduction of postzoster neuralgia (130), and reduction of gastrointestinal symptoms, fatigue, and pain in advanced cancer (22). The mechanistic rational is that such acute parenteral treatment targets massive inflammation-associated ROS generation and any side effects due to interference with physiological functions of ROS, such as in chronic oral therapy, are not observed.

A recent phase-I study investigating primarily safety of high-dose vitamin C infusion reported also positive effects on inflammation and endothelial function (39). However, endothelial function is only a surrogate parameter and hard outcome studies need to show true patient-relevant benefit. Prospective studies investigating the intravenous application of vitamin C in surgery and burn patients reported improved organ protection and function (83, 119, 142). On the other hand, preclinical studies prove that pharmacologic vitamin C concentrations are cytotoxic for cancer cell lines through the generation of H_2O_2.

There appears to be a multifactorial process where vitamin C induces cell cycle arrest, autophagy, apoptosis, and necrosis, depending on the cell genotype, the ascorbate concentration, and exposure time (113). The high (millimolar) concentrations necessary for this tumor cytotoxic effect can only be achieved intravenously because oral administration of vitamin C does not increase plasma levels above approx. 0.22 m*M* (84). There are currently three phase I/IIa studies being carried out in conjunction with the National Institutes of Health, which examine the effects of high-dosage vitamin C infusions adjuvant to standard therapy in the case of advanced tumors (93, 104, 152).

New Indirect Antioxidant Approaches

A different concept to antioxidant therapy follows the proposition that it is not the antioxidant molecules, but the antioxidant enzymes that provide relevant therapeutic benefit. Molecules that augment the physiological antioxidant response without being antioxidants themselves are here termed indirect antioxidants and include NRF2 agonists and resveratrol.

NRF2 activators

The transcription factor, nuclear factor (erythroid-derived 2)-like 2 (NRF2), is a master regulator of cell homeostasis that regulates the expression of antioxidant and cytoprotective genes that contain a specific enhancer sequence in their regulatory regions termed antioxidant response element (ARE). These genes account for more than 1% of the human genome and include antioxidant genes, *HMOX1* (coding heme oxygenase-1) and *NQO1* (coding NAD(P)H quinone oxidoreductase-1), and gene encoding enzymes involved in glutathione metabolism or in the generation of nicotinamide adenine dinucleotide phosphate (NADPH), *etc.* (Fig. 5A). For a detailed catalog of NRF2-regulated genes, see Hayes and Dinkova-Kostova (48).

Modulation of NRF2 activity may provide two advantages over direct antioxidants. First, the induction of NADPH, GSH, and thioredoxin metabolism is a natural system, resulting possibly in antioxidant activity in places where needed while leaving physiological ROS signaling intact. Second, because proteins have a longer half-life than small-molecule activators, the effect on the antioxidant defense may be more prolonged.

The main mechanism of regulation of NRF2 stability is its binding to the E3 ligase adapter kelch-like ECH-associated protein 1 (KEAP1) (Fig. 5B). This protein targets NRF2 for Cullin3/Rbx-mediated ubiquitination and subsequent proteasomal degradation. However, a drop in GSH concentration (characteristic of oxidant attack) or the presence of electrophiles leads to sulfhydryl bonding or adduct formation, respectively. This affects several cysteine residues in KEAP1, among which C151, C273, and C288 appear to be the most sensitive, probably because their pK_a value is lower (pK_a 4–5) compared with other cysteine residues (pK_a 8.5) (21, 91). Such modification of KEAP1 leads to disruption of its interaction with NRF2, its stabilization, nuclear translocation, and activation of about 250 ARE-containing genes.

All NRF2 agonists modify the sulfhydryl group of cysteine residues of KEAP1 by oxidation or adduct formation. These molecules include allyl sulfides, dithiolethiones, flavonoids, isothiocyanates, polyphenols, and terpenoids (49). However, electrophilic compounds may also react with redox-sensitive cysteine residues present in the catalytic center of several phosphatases. This interaction leads to upregulation of signaling pathways that further impinge on NRF2 activation. For instance, carnosol (96), tert-butylhydroquinone (127), synthetic triterpenoids (2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-imidazolide [CDDO; CDDO-Im]) (120), or nordihydroguaiaretic acid (126) activate AKT signaling.

Several reports demonstrate that phosphatase and tensin homolog (PTEN), which is mutated in a large number of human tumors, is a redox-sensitive phosphatase (78). Importantly, the catalytic C124 of PTEN can be modified through adduct formation with strong electrophiles such as CDDO-Im (120) and tert-buthylhydroquinone (127). This modification results in loss of its lipid phosphatase activity and yields a more sustained activation of signaling events downstream of PI3K. These events include the activation of NRF2 by preventing its degradation through a KEAP1-independent mechanism that involves its phosphorylation by glycogen synthase-3 and further ubiquitination by a β-TrCP/Cullin1/Rbx complex (Fig. 5C) (122, 123).

In summary, when considering electrophilic targeting to NRF2, it is important to remember that not only KEAP1 but also other redox-sensitive enzymes may cooperate to regulate this antioxidant pathway.

The most compelling evidence in favor of a role of NRF2 in prevention or protection from disease has been gathered from results obtained with NRF2 knockout mice. With increasing age, these mice present with chronic pathologies related to oxidant and inflammatory stress, including cognitive deficits (66), depressive disorder (97), and increased incidence of lupus-like autoimmune nephritis (92). In humans, many single-nucleotide polymorphisms have been identified in the coding and noncoding regions of the gene encoding NRF2, *NFE2L2*, and epidemiological studies have revealed significant associations of *NFE2L2* haplotypes with risks in pulmonary, gastrointestinal, autoimmune, and neurodegenerative diseases (27).

The most successful case reported so far of an indirect antioxidant targeting NRF2 is the ester derivative of fumaric acid, dimethyl fumarate (DMF). DMF crosses the gastrointestinal barrier, after which it is converted into the active principle monomethyl fumarate (MMF), which binds KEAP1. This binding disrupts the KEAP1/NRF2 interaction and leads to upregulation of the transcriptional NRF2

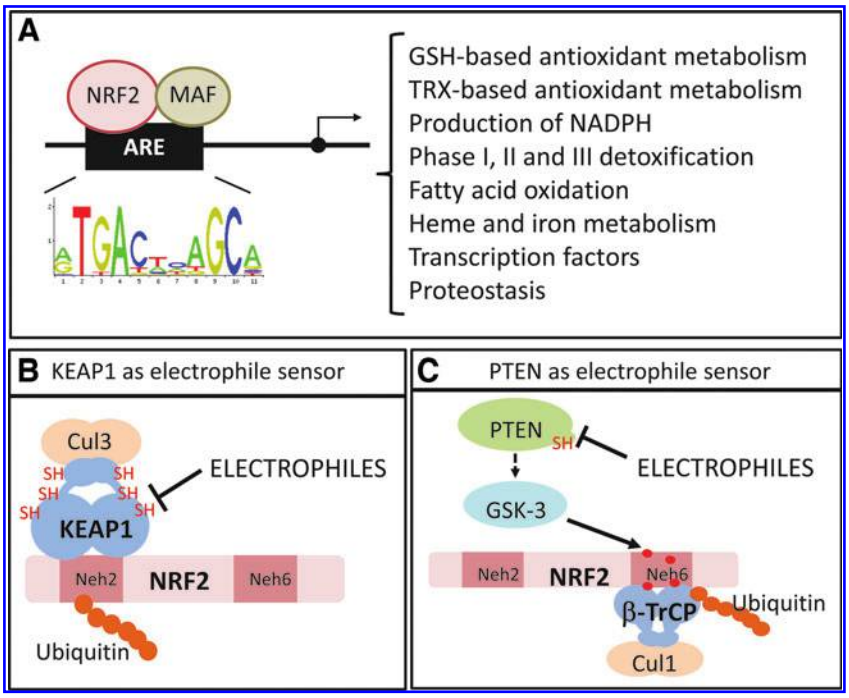

FIG. 5. Scheme on the antioxidant potential of the NRF2 signaling pathway and its pharmacologic targeting. (**A**) NRF2 is a basic region leucine zipper (bZip) transcription factor that makes dimers with proteins of the small MAF family. These heterodimers recognize an antioxidant response element (ARE) in about 250 genes (48). The consensus sequence is taken from JASPAR (99) (**B**) Regulation of NRF2/KEAP1 by electrophilic compounds. Under basal homeostatic conditions, NRF2 binds a KEAP1 homodimer through two tethering sites of low affinity (DLG) and high affinity (ETGE) located at the Neh2 domain. KEAP1 is a redox-sensitive E3 ligase adapter that leads to Cul3/Rbx-mediated ubiquitination of NRF2 and subsequent degradation by the proteasome. Adduct formation with electrophiles induces a conformational change in KEAP1 that prevents further degradation of NRF2 (145). (**C**) Regulation of NRF2/PTEN by electrophilic compounds. The lipid phosphatase activity of PTEN eliminates 3-phosphoinositides required to activate AKT, thus yielding glycogen synthase kinase-3 (GSK-3) active. GSK-3 phosphorylates NRF2 in several residues (DSGIS) of the Neh6 domain and creates a phosphodegron that is recognized by the E3 ligase adapter, β-TrCP. This process leads to a Cul1/Rbx-mediated ubiquitination and further proteasome degradation of NRF2. However, some electrophiles react with the critical C124 residue of PTEN located at the catalytic center to inhibit this enzyme. Then, 3-phosphoinositide levels remain high, leading to enhanced activation of AKT and inhibition of GSK-3. Under these conditions, NRF2 escapes GSK-3-mediated phosphorylation and recognition by the β-TrCP/Cul1/Rbx ubiquitin ligase (123, 127). AKT, protein kinase B; KEAP1, kelch-like ECH-associated protein 1; PTEN, phosphatase and tensin homolog. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

signature of antioxidant genes. Topical and oral administration of DMF (as a salt solution commercialized as Fumaderm) was indicated as early as year 1994 for the treatment of psoriasis before psoriasis was known to be an autoimmune disease or the molecular targets of DMF were identified (3).

The immunomodulatory effect of DMF has been exploited more recently for other autoimmune diseases such as lupus erythematosus (146), asthma, and arthritis (131), and a pharmaceutical formulation of DMF, termed FP187, is under development for use in autoimmune diseases.

DMF is being used in the treatment of relapsing–remitting multiple sclerosis (MS) (16). MMF is more potent than DMF in NRF2 activation, but the former is probably metabolized more rapidly. In an attempt to allow DMF to bypass gastric metabolism, it has been packaged in an oral delayed-release formulation known as BG-12. Following the success with BG-12 in two clinical trials, CONFIRM and DEFINE, this formulation has been commercialized as Tecfidera (16). Finally, a new formulation of MMF as a prodrug is currently in phase I trial for MS (61a).

Other lines of research have focused on targeting NRF2 in degenerative diseases with low-grade chronic inflammation using very potent synthetic triterpenoids that target KEAP1/NRF2. One of these compounds, CDDO-methyl ester (also known as bardoxolone methyl), was studied for therapy of diabetic nephropathy (151). The initial excitement about this compound was hampered by the observation that in the phase III clinical trial, termed BEACON, there was a small yet significant increase in heart failure in the treated arm compared with the placebo arm. This drawback was not related to NRF2 targeting, but rather to alteration of the endothelin signaling, leading to reduction in urine volume and sodium excretion in some patients with advanced chronic kidney disease (26). As a result, bardoxolone methyl is now being tested in pulmonary arterial hypertension (27a, 60), melanoma (54), and Friedreich's ataxia (27b). Moreover, its safety and efficacy for chronic kidney disease are being reevaluated (81a).

A third NRF2-activating principle is the isothiocyanate sulforaphane. Sulforaphane has been isolated from 3-day-old broccoli sprouts and other cruciferous vegetables as a product of the enzymatic cleavage of the glucosinolate, glucoraphanin, by the plant enzyme, myrosinase (37). Due to its electrophilic structure, sulforaphane interacts with specific

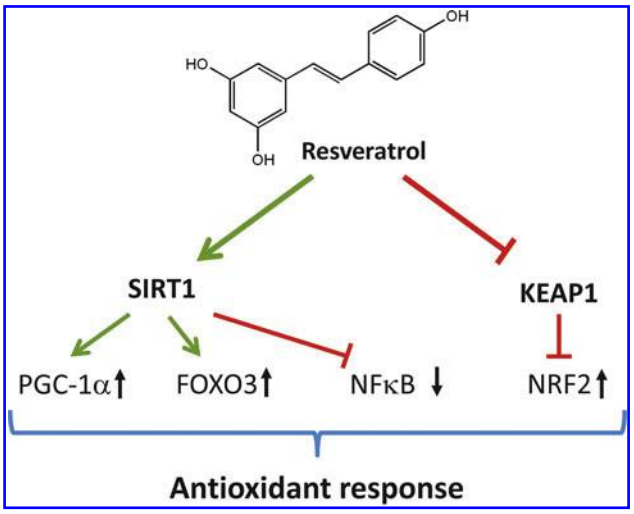

FIG. 6. Two mechanisms used by resveratrol to provide oxidant protection. SIRT1 is a histone deacetylase that participates in chromatin remodeling (not shown) and also in post-translational modification of transcription factors, such as PGC-1α, FOXO3a, and NF-κB. In addition, it inhibits KEAP1 and leads to NRF2 activation. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

redox-sensitive cysteine residues in KEAP1, including Cys151. This disrupts the Keap1/NRF2 complex and leads to the increase in NRF2 protein levels and transcriptional activity (31). Most clinical studies performed with sulforaphane have used a highly standardized formulation of broccoli sprout extracts. In contrast to DMF and bardoxolone methyl, a drawback of sulforaphane is the absence of a pure formulation that could be used clinically and the lack of commercial value that could attract the strong investment that pipelines on drug development require. Nevertheless, several attempts are being made to provide proof of concept that NRF2 targeting with sulforaphane has a therapeutic value. Currently, at least 32 studies assess its clinical efficacy in chronic diseases such as cancer, asthma, autism, schizophrenia, chronic kidney disease, type 2 diabetes, and cystic fibrosis.

Resveratrol

A comprehensive overview about resveratrol, including its targets and findings in clinical trials, is provided in a recent review (23) and schematized in Figure 6. The antioxidant phytochemical resveratrol was initially viewed as a direct ROS scavenger, but recent data suggest that its beneficial effects—if any—are rather mediated by indirect antioxidant mechanisms (85). Resveratrol increases the expression of antioxidant enzymes, such as SODs, catalase, glutathione peroxidase, and others, and reduces the expression of the ROS-forming NADPH oxidase type 4 (NOX4) (139).

In addition, resveratrol confers antioxidant activity by induction of the NRF2-heme oxygenase-1 pathway (69, 70) and it restores the activity of eNOS by increasing the synthesis of its cofactor, tetrahydrobiopterin (BH_4) (155). There is also good evidence that resveratrol not only acts on gene expression *via* miRNAs as well as epigenetic modifications *via* activation of the NAD^+-dependent deacetylase sirtuin 1 (SIRT1) (38, 85, 105) but also on proteins of the DNA repair machinery, thereby contributing to genome stability (41).

The most compelling clinical studies on the use of resveratrol in antioxidant therapy have demonstrated a reduction in redox biomarkers together with an increase in the NRF2 signature (42). In some cases, preliminary evidence of a salutary effect has been reported. Thus, resveratrol improves insulin sensitivity in patients with type 2 diabetes (19). In obese humans, resveratrol supplementation induced metabolic changes mimicking the effects of calorie restriction (144). Resveratrol demonstrated anti-inflammatory, antioxidant, and hypotriglyceridemic effects in healthy smokers (15). Further phase III studies will be required to determine real efficacy of this indirect antioxidant.

Conclusions

In view of the disparate results obtained with antioxidant compounds ranging from possibly beneficial to many futile to some harmful effects, it is necessary to reevaluate antioxidant therapy with a revised concept of oxidative stress that considers not only over ROS imbalance in a quantitative manner but also the molecular nature of ROS local cellular and tissue production and the enzymatic machinery in charge of its regulation.

While chronic, not indicated, therapy with antioxidants (especially lipid-soluble ones) must clearly not be recommended, there may be potential for the use of selective antioxidants, such as vitamin C, in situations of deficiencies or short-term overproduction accessible to parenteral high-dose therapy. Whether there is room for SOD mimetics needs to be shown.

More modern indirect antioxidants that target redox enzymes seem to be the more promising. NRF2 agonists may have the benefit of not causing reductive stress, but instead to upregulate endogenous antioxidant defense systems. Other approaches such as interfering with specific ROS-producing enzymes directly or even functionally repairing ROS-induced damage are discussed in another review of this Forum (see Targets review in the same Forum). Time and clinical trials investigating patient-relevant outcomes will tell.

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Author Disclosure Statement

Claudia Vollbracht is a part-time employee of Pascoe Pharmazeutische Präparate GmbH, Giessen, Germany, which markets parenteral vitamin C products. Dennis Riley is the Chief Scientific Officer of Galera Therapeutics, Inc. (Malvern, PA), which is developing GC4419, an SOD mimetic. For all other authors, no competing financial interests exist.

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Abbreviations Used

AKT = protein kinase B
ARE = antioxidant response element
BH_4 = tetrahydrobiopterin
BO-653 = 2,3-dihydro-5-hydroxy-2,2-dipentyl-4,6-di-tert-butylbenzofuran
CDDO; CDDO-Im = 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-imidazolide
CVD = cardiovascular disease
DMF = dimethyl fumarate
eNOS = endothelial nitric oxide synthase
ERK = extracellular signal-regulated kinases
$gp91^{phox}$ = 91kDa membranous subunit of the phagocyte NADPH oxidase (Nox2)
GSH = glutathione
H_2O_2 = hydrogen peroxide
JNK = c-Jun N-terminal kinases
KEAP1 = kelch-like ECH-associated protein 1
MAPK = mitogen-activated protein kinase
miRNA = microRNA, a small noncoding RNA molecule
mitoTEMPO = (2-(2,2,6,6-Tetramethylpiperidin-1-oxyl-4-ylamino)-2-oxoethyl)triphenylphosphonium chloride monohydrate
MMF = monomethyl fumarate
MS = multiple sclerosis
NAC = N-acetylcysteine
NADPH = nicotinamide adenine dinucleotide phosphate
$^{\bullet}NO$ = nitric oxide
NOS = nitric oxide synthase
NOX = nicotinamide adenine dinucleotide phosphate oxidases (1, 2, 4 isoforms)
NRF2 = nuclear factor (erythroid-derived 2)-like 2
NXY-059 = disufenton sodium, a synthetic antioxidant
$O_2^{-\bullet}$ = superoxide anion
p38 = p38 mitogen-activated protein kinases
PGC1α = peroxisome proliferator-activated receptor gamma coactivator 1α
PTEN = phosphatase and tensin homolog
ROS = reactive oxygen species
SOD = superoxide dismutase

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