Review

Oxidative Stress and Its Role in Skin Disease

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ABSTRACT

Skin is a major target of oxidative stress due to reactive oxygen species (ROS) that originate in the environment and in the skin itself. ROS are generated during normal metabolism, are an integral part of normal cellular function, and are usually of little harm because of intracellular mechanisms that reduce their damaging effects. Antioxidants attenuate the damaging effects of ROS and can impair and/or reverse many of the events that contribute to epidermal toxicity and disease. However, increased or prolonged free radical action can overwhelm ROS defense mechanisms, contributing to the development of cutaneous diseases and disorders. Although ROS play a role in diseases such as skin cancer, their biological targets and pathogenic mode of action are still not fully understood. In addition, strategies useful in the therapeutic management of ROS action in human skin are still lacking. This review is intended to give investigators an introduction to ROS, antioxidants, two skin disorders influenced by ROS action (skin cancer and psoriasis), and relevant model systems used to study ROS action. Antioxid. Redox Signal. 4, 665–673.

INTRODUCTION

The skin is a biological barrier that defends against multiple environmental insults. Free radicals, one form of insult, induce or contribute to adverse effects on the skin, including erythema, edema, wrinkling, photoaging, inflammation, autoimmune reactions, hypersensitivity, keratinization abnormalities, preneoplastic lesions, and skin cancer (56). Pollution, atmospheric gases, ultraviolet (UV) radiation, microorganisms, viruses, and xenobiotics all serve as sources of exogenously or environmentally derived free radicals (22), whereas endogenous radicals are generated during normal cellular metabolism, immune reactions, and under pathological conditions (62). Reactive oxygen species (ROS) are a family of oxygen-based free radicals that contain or are capable of producing an unpaired electron. ROS are produced during the reduction of molecular oxygen in the intermediate steps:

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\begin{align*}
O_2 + ?e^- + H^+ & \rightarrow H_2O \rightarrow H^+ + O_2^- \\
H_2O + ?e^- + H^+ & \rightarrow H_2O_2 \\
H_2O_2 + ?e^- + H^+ & \rightarrow H_2O + OH^- \\
OH^- + ?e^- + H^+ & \rightarrow H_2O
\end{align*}
\]

At low levels, superoxide anion (\(O_2^-\)), hydroxyl radicals (OH\(^-\)), hydrogen peroxide (H\(_2\)O\(_2\)), and molecular oxygen (O\(_2\)) take part in numerous cellular processes, including cell proliferation, apoptosis, immune responses, and cell differentiation. Overproduction or inadequate removal of ROS can result in oxidative stress, leading to altered metabolism, dysregulated signal transduction events, and biomolecular damage, all of which contribute to pathological changes in cell and tissue function. Biomolecular damage that occurs as a result of elevated ROS levels is manifested as lipid peroxidation, DNA

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mutations/breakage, enzyme inactivation/activation, and protein oxidation/degradation (51). This damage is often secondary to the production of reactive biomolecules (e.g., hydroxynonenal and malondialdehyde) that arise as the result of ROS action (57). The action of reactive biomolecules, thus, serves to exacerbate the damaging effects of ROS.

ATTENUATION OF ROS ACTION

Antioxidants function to delay or prevent ROS-induced cellular damage, and work by reducing local oxygen concentrations, impairing chain initiation reactions, binding catalysts such as metal ions that generate ROS, and attenuating hydrogen abstraction by active radicals (65). They include low-molecular-weight compounds such as β-carotene, ascorbate, tocopherols, uric acid, the thiol-containing compound glutathione (GSH), as well as high-molecular-weight antioxidant enzymes, and proteins such as metallothionein and ferritin.

The low-molecular-weight antioxidants β-carotene (vitamin A) and ascorbate (vitamin C) attenuate the damaging effects of O$_2^\cdot$ in lipid and nonlipid cellular compartments. Cytosolic ascorbate takes part in the continuous regeneration of tocopherol (vitamin E) (80), demonstrating the cooperative relationship between cellular antioxidant synthesis. The primary function of tocopherol is to prevent lipid peroxidation chain reactions and quench O$_2^\cdot$ in cellular lipid compartments (12). Uric acid protects against oxidative damage by scavenging O$_2^\cdot$, OH\(^\cdot\), and other cellular oxidants (6). GSH, an important water-phase antioxidant and essential cofactor for antioxidant enzymes, contributes to the recycling of oxidized antioxidants, and serves as a scavenger of O$_2^\cdot$ and OH\(^\cdot\) (65).

Major high-molecular-weight cellular antioxidant enzymes and proteins that modulate the action of ROS or their by-products include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), the thioredoxin/thioredoxin reductase system, metallothioneins, and ferritin (80). SOD (mitochondrial manganese SOD and cytoplasmic copper-zinc SOD) inactivates O$_2^\cdot$ by converting it to H$_2$O$_2$, whereas CAT inactivates H$_2$O$_2$ via its dissociation to water and oxygen. GPx, in the presence of reduced glutathione (GSH) also converts H$_2$O$_2$ to water. In the latter reaction, GSH is converted to its oxidized form (GSSG), and subsequently regenerated from GSSG by GR (19). The thioredoxin/thioredoxin reductase system quenches free radicals and functions in the recycling of oxidized ascorbate (3). Functionally, thioredoxin reductase reduces oxidized thioredoxin in the presence of NAD(P)H. Reduced thioredoxin then serves as an electron donor for thioredoxin peroxidase, which reduces H$_2$O$_2$ to water (68). Metallothioneins, a family of zinc-binding proteins, act as antioxidants. Their functions include free radical/transition metal sequestering, regulation of zinc homeostasis, and interactions with GSH (66). In general, iron (Fe$^{2+}$) plays a key role in antioxidant enzyme function where it acts as a catalyst during the reduction of H$_2$O$_2$ to OH$^-$ (40). Cellular levels of Fe$^{2+}$ are maintained at a minimum to avoid excessive production of OH$^-$ via the Fenton reaction (Fe$^{2+}$ + H$_2$O$_2$ $\rightarrow$ Fe$^{3+}$ + OH$^-$ + OH$^-$). This is accomplished in part by the iron storage protein ferritin, which limits the catalytic availability of Fe$^{2+}$ for participation in oxygen radical generation (79).

ROS-MEDIATED SKIN CANCER INDUCTION

ROS-induced DNA damage

It is well known that oxidative stress contributes to skin carcinogenesis, especially following UV irradiation (31). Some of the deleterious events that occur in cells following ROS exposure include DNA damage, cell-cycle dysregulation, DNA repair and/or replication disturbance, and gene mutations. ROS-induced DNA damage also induces the production of immunosuppressive cytokines and immune suppression that may contribute to the emergence of skin cancer (Fig. 1).

ROS-induced DNA damage includes mutations in growth regulatory genes that lead to loss of cell-cycle control and DNA repair and contribute to abnormal apoptosis. An example is the tumor suppressor p53, which regulates multiple growth inhibitory and apoptotic genes. ROS action results in loss of function mutations in the p53 gene, resulting in abnormal cell function (64). ROS, moreover, regulate p53 in a posttranslational manner via reduction or oxidation of intramolecular disulfide bonds, rendering wild-type p53 a conformational mutant, i.e., producing a similar biological outcome as p53 mutations (47). Research indicates that treatment of mice with the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA), UV radiation, or tumor-promoting phorbol esters induces H$_2$O$_2$ generation and the formation of oxidized bases in epidermal DNA (85) that may contribute to mutations in p53 and other genes. Events of this type are not limited to rodents at high levels of 8-hydroxy-2′-deoxyguanosine DNA adducts (8-HO$_2$G), a by-product of OH$^-$ attack on DNA, appear in normal human epidermis following UV irradiation (1). Other forms of DNA damage associated with ROS activity [e.g., cyclobutyl pyrimidine dimers and (6-4) photoproducts] also occur in the skin of humans who have increased sensitivity to UVB radiation (81), and in organ-cultured human skin exposed to UVB radiation (55).

Antioxidants attenuate cancer induction and/or its development, indicating that ROS-induced DNA damage can be controlled pharmacologically (73). Examples include tocopherol and epigallocatechin gallate, a green tea polyphenol that protects skin from oxidative stress, both of which delay the onset of radiation-induced skin cancer in rodents (25). In vitro, treatment of mouse keratinocytes with ascorbic acid, Trolox (a water-soluble form of tocopherol), or selenite (a known antioxidant) results in a significant decrease in the number of detectable UVB radiation-induced 8-OH$_2$G adducts (77). This effect is not consistent across experimental systems because ascorbate, tocopherol, or depletion of endogenous GSH lowers cellular sensitivity to UVB radiation-induced oxidative damage in immortalized HaCaT keratinocytes. However, the DNA-damaging effects of UVA radiation can be countered by pretreatment with the same antioxidants in HaCaT keratinocytes (39).
ROS-induced immune system modulation

Skin cancer development depends on immune surveillance breakdown mediated in part by ROS action. UV irradiation, for instance, produces a number of adverse effects on the immune system, including suppression of systemic and cutaneous immune responsiveness, and immunologic unresponsiveness to cutaneous tumors (32). ROS-induced immune modulation revolves around DNA, as it is one of the primary molecular targets associated with immune dysfunction in the skin. ROS generate DNA damage that correlates with a reduction in contact sensitization, an impaired ability of dendritic cells in the draining lymph nodes to present antigen, and the development of hapten-specific suppressor T lymphocytes (82). Evidence that DNA damage is a contributing event in immune system suppression comes from studies utilizing liposomes containing T4 endonuclease V, an enzyme that repairs cyclobutyl pyrimidine dimers (33), or photolyase, an enzyme that splits radiation-induced cyclobutyl pyrimidine dimers (83). The activity of photolyase, for example, reduces the immune suppressing effects of UV irradiation as measured by a reduction in contact hypersensitivity, impairment in antigen-presenting cell function, and the induction of transferable immune suppression (82).

Antioxidant studies demonstrate that ROS-induced immunosuppression can be modulated. For example, immune suppression following UV irradiation permits the outgrowth of developing skin tumors, an effect attenuated by tocopherol (75). In humans, high-dose tocopherol combined with ascorbate results in a reduction in radiation-induced immune suppression (20). Protection against this effect, evaluated by suppression of epidermal contact hypersensitivity in mice, also occurs following exposure to green tea polyphenol extracts (30). In vitro, tocopherol attenuates radiation-induced oxidative events and immune suppression in isolated epidermal cells, monitored by measuring lipid peroxidation, and lymphocyte proliferation induced by epidermal cells or purified Langerhans cells in mixed epidermal cell–lymphocyte cultures (14). GSH, similar to low-molecular-weight antioxidants, also protects against local and systemic immune suppression that may contribute to skin cancer induction by UVB radiation (74).

THE DUAL ROLE OF ROS IN PSORIASIS

Excessive generation of ROS by the immune system results in pathological changes that contribute to inflammatory disorders such as scleroderma and psoriasis (17). Psoriasis is characterized by elevated keratinocyte proliferation, abnormal keratinocyte differentiation, alterations in dermal vasculature, elevated cellular antioxidant activities, and the presence of dermal/epidermal T cells, monocytes/macrophages, and polymorphonuclear leukocytes (PMNs) within or near psoriatic lesions (16).

ROS contribute to the development and/or maintenance of psoriasis in a numbers of ways. Figure 2 depicts several...
cellular events, proposed to be important in psoriasis, that are influenced by ROS action. PMNs, for example, secrete $\text{O}_2^-$ and $\text{H}_2\text{O}_2$ during respiratory bursts that result in the elevated ROS levels within the skin (52). Altered antioxidant levels occur in a variety of cell types residing within psoriatic lesions, providing further evidence that ROS, either directly or indirectly, influence endogenous detoxification mechanisms. Elevated interleukin (IL)-1β and tumor necrosis factor-α (TNF-α)-induced SOD expression occurs in psoriatic lesions in vivo and in cultured human keratinocytes in vitro, demonstrating a relationship between proinflammatory cytokine expression and ROS level/activity (42). Under normal conditions, elevated SOD expression is a protective response mediated by cytokines released from inflammatory cells invading diseased skin. However, high or long-term SOD expression can result in the inappropriate production of ROS such as $\text{H}_2\text{O}_2$ in intra- and extracellular compartments (49). Indeed, TNF-α-enhanced SOD activity, $\text{O}_2^-$ generation, and $\text{H}_2\text{O}_2$-mediated complement activation occur in fibroblasts (71), and may contribute to inflammation and tissue damage at the site of psoriatic skin lesions.

At the molecular level, cross-talk between protein kinase C (PKC) and protein kinase A (PKA) functions in part to down-regulate respiratory bursts in PMNs and release of ROS (67). Dermal fibroblasts in vitro also display decreased PKA activity, measured by catalytic subunit binding, following exposure to $\text{O}_2^-$ and $\text{H}_2\text{O}_2$ (63). PKA activity is reduced in psoriatic fibroblasts in vivo (11), suggesting that ROS, at the molecular level, serve to alter fibroblast PKA activity and cyclic AMP binding. Down-regulation of PKA activity is significant because in normal fibroblasts and other cell types, elevation of intracellular cyclic AMP (i.e., elevated PKA activity) is inhibitory to cell growth and division (58). Indeed, ROS stimulate cell proliferation and trigger undifferentiated keratinocytes into forming a defective stratum corneum, an event central to the development of psoriasis (69). Abnormal keratinocyte growth in psoriasis, thus, may be the partial result of elevated $\text{O}_2^-$ generated by PMNs, and psoriatic dermal fibroblasts (18).

In contrast to their pathological role in psoriasis, ROS appear to be of benefit in the therapeutic management of this disorder. Oxidative stress generation following exposure to dithranol (anthralin), a widely used antipsoriatic drug with tumor-promoting and skin-irritation properties, indirectly suggests that ROS contribute to the therapeutic effects of antipsoriatic compounds (45). Oxidative stress generation at the site of anthralin treatment also correlates with increased production of the proinflammatory cytokines granulocyte macrophage stimulating factor (GM-CSF), IL-6, IL-8, and TNF-α, all of which may enhance immune system function necessary for disease attenuation (35). Anthralin-induced cytotoxicity in primary epidermal keratinocytes, evaluated by changes in plasma membrane integrity, lysosomal function, and mitochondrial metabolic activity, indicates that $\text{O}_2^-$ and $\text{H}_2\text{O}_2$ contribute to the therapeutic effects of this compound (24), possibly via the loss of glucose-6-phosphate dehydrogenase activity (54). Anthralin potently inhibits human monocyte $\text{O}_2^-$ generation (53), further demonstrating that this
drug blunts respiratory bursts involved in the etiology of psoriasis.

Antioxidants, including tocopherol, ameliorate nonspecific ROS toxicity, demonstrated by the selective inhibition of erythema and hyperpigmentation that occurs following psoralen (furocoumarins) treatment of psoriasis (61). Antioxidant-attenuated toxicity may be due to tocopherol interfering with free radical formation rather than by scavenging antrahin radicals directly (60). SOD and tocopherol also reduce the damaging side effects of antrahin-induced ROS action without loss of therapeutic efficacy (34). Although antioxidants diminish the nonspecific toxicity of antrahin-induced ROS, it is unknown if these agents can impair or reverse changes in cell structure and function mediated by ROS. Partial support for the latter has been suggested by Raynaud et al., who demonstrated that small molecular weight and enzymatic antioxidants attenuate PKA activity modulated by ROS (63).

MODEL SYSTEMS IN WHICH TO STUDY ROS ACTION

Animal and cell-culture models provide a powerful approach in which to elucidate the contribution of ROS to a variety of skin diseases and disorders. Some of these experimental systems have not been engineered or traditionally used to examine the role of ROS in skin; however, this should not rule out their application in research designed to elucidate the pathological effects of ROS.

In vivo models

The SKH-1 hairless mouse has been used extensively in antioxidant and ROS research. Studies performed by Lopez-Torres et al. in SKH-1 mice suggest that continuous damage to skin by free radicals occurs during the lifetime of an organism (43). In a comparative study using SKH-1 mice, it was found that human skin is more susceptible to free radical formation, an effect that might be due in part to a unique visible light chromophore found in human skin (27). The dose-response effects of acute UV irradiation on dermal/epidermal antioxidant levels including CAT, GPx, GR, ascorbate, and GSH in SKH-1 mice indicate that the antioxidant capacity of the epidermis is greater than that of dermis (70). Tocopherol blunts radiation-induced ROS action via its ability to elevate dermal SOD activity and protect epidermal GPx and SOD from depletion in this model (43). Similarly, tocopherol sorbate, α-tocopherol, and tocopherol acetate decrease free-radical formation in SKH-1 mouse skin (28). Other effects of ROS in SKH-1 mice have been evaluated, including the induction of epidermal DNA damage (50), antioxidant effects on skin carcinogenesis (8), and epidermal immune system modulation (76).

Although the reason(s) for its increased sensitivity to ROS action has not been elucidated, the inbred SENCAR (SENSitivity to CARCinogenesis) strain of mice has been used to examine oxidant involvement and the preventative effects of antioxidants in skin tumor promotion, oxidative stress generation, and inflammation (86). For example, the flavonoid compound silymarin, derived from the milk thistle plant (Silybum marianum), is thought to be protective against UV radiation-induced skin cancer. Studies in SENCAR mice demonstrate the inhibitory effects of this compound on tumor promotion, oxidative stress generation, and inflammatory responses (86). Tumor promotion inhibition with other naturally occurring compounds, including nordihydroguaiaretic acid and diallyl sulfide antioxidants (5), as well as polyphenolic fractions (isolated from green tea), also has been evaluated in the SENCAR mouse model (29).

Transgenic antioxidant-deficient or -overexpressing mice provide a unique opportunity to modulate antioxidant activity in vivo without pharmacological manipulation. The tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) induces oxidative damage to DNA and decreases the activity of several antioxidant enzymes, including GPx. Transgenic animals that express inducible GPx display pronounced GPx induction and no loss of GPx activity, as compared with non-transgenic control mice, following TPA exposure (9). Carcinogenic responses to initiation by DMBA and promotion with TPA have been evaluated in C57 transgenic mice (C57BL/6 × CBA/J) that overexpress SOD and GPx (44). In this study, overexpression of skin antioxidant enzymes leads to increased, rather than decreased, tumorigenesis in a two-stage skin carcinogenesis model, and may provide support for the prooxidant nature of cellular enzymatic antioxidants.

The Tg.AC transgenic mouse carries the coding sequence of v-Ha-ras linked to a ζ-globin promoter and an SV40 polyadenylation signal sequence (23). Tg.AC mice develop skin papillomas, dependent on v-Ha-ras transgene activity, in response to topically applied genotoxic and nongenotoxic carcinogens and tumor promoters. One study examining ROS action in Tg.AC mice indicates that inducible nitric oxide synthase, an enzyme that contributes to oxidative stress generation, is up-regulated following tumor promotion with TPA (37). Experiments designed to elucidate the effect of UV irradiation on tumorigenesis in Tg.AC mice indicate that p53 mutations or protein loss is not a common occurrence during the induction of photocarcinogenesis (78). The latter suggests that the Tg.AC mouse may be an appropriate model for skin cancers that have a ROS component, but do not display mutations in p53 [e.g., arsenic-induced skin cancer (13)].

In vitro models

In vitro, keratinocyte, fibroblast, and melanocyte cultures are appropriate epidermal models that can be used to determine cellular and biochemical details of ROS action. For example, immortalized human HaCaT keratinocytes have been used to examine mitochondria ROS accumulation (21) and the effects of the oxidizing agents and their immune-modulating role in allergic contact dermatitis (41) and in radiation-induced antioxidant defense regulation (36). Cellular sensitivity to ROS production, effects on apoptosis, and antioxidant cell defense, following Bcl-2 overexpression, also have been evaluated in HaCaT keratinocytes (84). In immortalized mouse HEL30 keratinocytes, arsenic induces concentration- and time-dependent increases in cellular oxidative activity (15). This effect is attenuated by rotenone pretreatment, suggesting the involvement of mitochondria-derived ROS in the overexpression of growth factors that play a role.
in arsenic-induced skin hyperkeratoses, cancer (15), and possibly other diseases.

Although displaying a finite life span, primary human keratinocytes, fibroblasts, and melanocytes provide realistic in vitro models in which to examine oxidative effects on cutaneous function. Primary human keratinocytes have been used to examine the role of oxidative stress in redox cycling (72) modulation of mitogenic, inflammatory, and apoptotic signal transduction (4). Primary human dermal fibroblast studies suggest that ROS play an active role in oxidative stress-induced connective tissue damage (10), heme oxygenase-1 induction, and its role in cellular Fe²⁺ homeostasis (2). Studies using human melanocytes demonstrate the differential sensitivity of melanocytes and melanoma cells to H₂O₂-induced oxidative stress (48), melanogenesis, and its regulation by GSH (7). The relationship between cell death and increased sensitivity to oxidative stress in vitiligo melanocytes in vitro (26) and imbalance in the antioxidant system in these cells (46) provide further support for ROS-mediated damage as a pathogenic event in melanocyte degeneration.

In vitro skin equivalent models have come into favor in recent years when performing studies where cell–cell interactions may be critical. Skin equivalents are prepared by culturing human keratinocytes on fibroblasts embedded in collagen gel that closely resembles human skin (38). One study examining antioxidant depletion in a skin equivalent model demonstrates that UVA and UVB irradiation depletes cellular tocopherol and ascorbate, and this correlates with detectable oxidative damage (59).

**PERSPECTIVE**

ROS play a dual role in the development of skin disease and disorders. Genetic alterations leading to abnormal cell function and immune suppression following ROS exposure are likely to permit the development of skin disease, such as cancer, over the lifetime of an individual.

Taken together, the evidence presented here and elsewhere in the literature demonstrates that oxidative mechanisms play a role in the pathogenesis of skin disorders and disease. Research indicates that antioxidants offer protection against the damaging effects of oxidative stress in vitro and in vivo. There is considerable interest in determining whether agents with antioxidant properties can be of benefit in preventing the onset or progression of skin pathologies in human beings. Thus, reliable data regarding the benefits of antioxidant supplementation will emerge from continued basic research, clinical, and epidemiological studies.

**SUMMARY**

ROS are agents that play a role in both normal and abnormal epidermal physiology. This review is an attempt to discuss briefly various aspects of excessive free radical action, targets, and attenuation in biologically relevant model systems. Oxygen radicals are generated during normal metabolism and are an integral part of cellular function (e.g., immune-mediated destruction of bacteria and virus-infected cells, inhibition of tumor cell growth, and cytochrome P450-mediated chemical detoxification). The generation of ROS usually has little consequence because of a vast array of protective intracellular defenses in the skin. However, under certain circumstances, increased ROS production can overwhelm the cellular defense mechanisms used to detoxify these species.

Important reactants in cells are oxygen and its radical derivatives, including O₂⁻, OH⁻, and H₂O₂. The skin has developed a comprehensive array of defenses that prevent ROS formation or limit their damaging effects, including both enzymatic and nonenzymatic antioxidants. ROS formed within cells can oxidize biomolecules resulting in DNA damage, lipid peroxidation, and enzyme dysfunction that contribute to cellular toxicity, pathology, or death. The end result of chronic, elevated exposure to ROS is changes in cell function that contribute to skin cancer and psoriasis. The use of sensitive or transgenic animal models will help in further delineating the effects of ROS in these disorders and others.

Many questions remain to be answered concerning the physiological effects of ROS. It is anticipated that continued research will increase knowledge concerning the role of ROS in skin disease, and continue to shed light on therapeutic strategies that can be used to reduce or eliminate cutaneous pathophysiology.

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**ABBREVIATIONS**

CAT, catalase; DMBA, 7,12-dimethylbenz[a]anthracene; GM-CSF, granulocyte macrophage stimulating factor; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; H₂O₂, hydrogen peroxide; IL, interleukin; O₂⁻, superoxide anion; OH⁻, hydroxyl radical; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; PKA, protein kinase A; PKC, protein kinase C; PMN, polymorphonuclear leukocyte; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TPA, 12-O-tetradecanoylphorbol 13-acetate; UV, ultraviolet.

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