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Research Article

OXIDATIVE STRESS VERSES SKIN HYPERPIGMENTATION

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Abstract

Skin is a major target of toxic agents, capable of altering its structure and function. Many environmental pollutants are either itself oxidants or catalyze the production of reactive oxygen species (ROS) directly or indirectly. Cellular antioxidant enzymes and free radical scavengers normally protect a cell from toxic effects of the ROS. However, ROS overtakes the antioxidants defense of cells, oxidative damage of the cellular macromolecules (lipids, proteins and nucleic acids) occurs. ROS- medicated lipid peroxidation, protein oxidation, and DNA damage are well known outcomes of oxygen derived free radicals. Present study tells us the mechanism of ROS-mediated oxidative damage of protein, lipids and nucleic acids.

Key Words: Melasma, Oxidative stress, Hyperpigmentation, Reactive oxygen species.

INTRODUCTION

Melasma (derived from the Greek word, '*melas*' meaning black) is a common, acquired, circumscribed hypermelanosis of sun-exposed skin. It presents as symmetric, hyperpigmented macules having irregular, serrated, and geographic borders. The most common locations are the cheeks, upper lips, the chin, and the forehead, but other sun-exposed areas may also occasionally be involved. It is much more common in women during their reproductive years but about 10% of the cases do occur in men (Bandyopadhyay, 2009).

Of the many causes of melasma, oxidative stress (OS) has been identified as one factor that affects individual's status and thus, has been extensively studied in recent years. Melanocytes like any other aerobic cell are constantly facing the "oxygen-paradox". Oxygen is essential to sustain life as physiological levels to maintain normal cell function. Conversely, breakdown products of oxygen such as ROS can be detrimental to cell function and survival (Bandyopadhyay, 2009). Reactive oxygen species are present as free radicals like hydroxyl ion, superoxide, hydrogen peroxide, peroxyl radical, and hypochlorite ion etc.

OS is a consequence of an imbalance between the production of ROS and the body's antioxidant defense mechanisms. OS also has been implicated in the pathogenesis of many other human diseases such as atherosclerosis, cancer, diabetes, liver damage, rheumatoid arthritis, cataracts, AIDS, inflammatory bowel disease, central nervous system disorders, Parkinson's disease, motor neuron disease.

SOURCE OF ROS

ROS includes a collection of radical (hydroxyl ion, superoxide, nitric oxide, peroxyl, etc.) and non-radical (ozone, singlet oxygen, lipid peroxide, hydrogen peroxide) oxygen derivatives (Briganti S and Picardo M, 2003). These derivatives participate in a cascade of reactions that give rise to free radicals that ultimately can damage organic substrates. Reactive nitrogen species (nitrous oxide, peroxynitrite, nitroxyl ion, etc.) are also a class of free radicals derived from nitrogen and considered a subclass of ROS (Roberts MJ, Wondrak GT *et al*, 2003; Sikka SC, 2001).

Electron acceptors such as molecular oxygen react readily with free radicals to themselves become free radicals. An additional source of oxygen radicals in skin as well as in other organs is infiltrating activated leukocytes that possess abundant systems capable of generating these species, among which $O_2^{\cdot-}$ and hypochlorite are important sources of ROS in situ. The fundamental purpose of the release of large amounts of ROS during the inflammatory process is to kill or destroy invading microorganisms and/or to degrade damaged tissue structures. It is the imprecise targeting of ROS that can induce oxidative stress in adjacent normal cells leading to enhancement of

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pathologic processes (Cerutti *et al*, 1992).

PHYSIOLOGICAL ROLE OF ROS IN SKIN HYPERPIGMENTATION

Skin exposure to many environmental pollutants like gaseous airborne, UV radiation, food contaminants/additives/preservatives, cosmetic products, drugs, etc are either themselves oxidants or catalyze the production of reactive oxygen species (ROS) directly or indirectly. ROS are believed to activate proliferative and cell survival signaling that can alter apoptotic pathways that may be involved in the pathogenesis of a Melasma (Athar, 2002). In addition, heme pathway intermediates have pro-oxidant effects; intrinsically generate ROS or their metabolites such as redox active quinones (Briganti and Picardo, 2003).
UV exposure to the skin results in generation of reactive oxygen species (Cross, Halliwell and Borish, 1987). ROS are constantly generated in keratinocytes and fibrocytes, and are rapidly removed by nonenzymic and enzymic antioxidant substances.

Reactive nitrogen species (nitrous oxide, peroxynitrite, nitroxyl ion, etc.) are also a class of free radicals derived from nitrogen and considered a subclass of ROS. Reactive nitrogen species (RNS) are generated as a result of sequential reactions that begin with nitric oxide synthase (NOS)-mediated conversion of arginine to citrulline. In this reaction, NO is generated, which reacts with O_{2^-} to produce peroxynitrite (ONOO-) (Sikka SC, 2001).

Exposure of skin to a number of chemical and physical environmental agents induces oxidative stress leading to induction of cutaneous lipid peroxidation with concomitant modulation in the levels of antioxidant and drug-metabolizing enzymes (Bickers *et al*, 1982; Das *et al*, 1985; Connor and Wheeler, 1987). In later studies, it was demonstrated that UV generated ROS affect mitogen-activated protein kinase (MAPK) signaling cascades (Inal ME *et al*, 2001; Thiele J *et al*, 2001). These activate the nuclear factor kappa B(NF-$^{\kappa}$B) as well as c-jun N-terminal and p38 MAP kinase followed by activation of a number of transcription factors such as activator protein 1 (AP-1) (Dhar *et al*, 2002). Both may contribute to the induction of heme oxygenase-1 (HO-1) and matrix metalloproteinases (MMPs) in the skin. Recently, Reelfs *et al* (2004) have shown that increased level of HO-1 may elevate cellular levels of iron that can promote further ROS generation. MMPs induction leads to enhanced degradation of extracellular matrix proteins that favor wrinkle formation and metastasis. In addition, the mitogen-activated protein kinase (MAPK) pathway is a target of oxidative stress (Kim AL *et al*, 2005). It is interesting to note that solar UV radiation, a major cause of oxidative stress in skin, also influences these pathways in ways that closely mimic ROS. These reactive oxygen species generate following UV induced damage to the epidermis and are cytotoxic to melanocytes and also inhibit tyrosinase (Jayanth DP *et al*, 2002)

LIPID PEROXIDATION

Lipids are considered to be the most susceptible macromolecules and are present in dermal plasma membrane in the form of polyunsaturated fatty acids (PUFA), fatty acids that contain more than two carbon-carbon double bonds. ROS attacks PUFA in the cell membrane, leading to a cascade of chemical reactions called lipid peroxidation. ROS have a tendency toward chain reactions; that is, a compound carrying an unpaired electron will react with another compound to generate an unpaired electron, in such a manner that "radical begets radical". The reactions proceed through three main steps--initiation, propagation, and termination (Briganti and Picardo, 2003).

During initiation, the free radicals react with fatty acid chains and release lipid free radicals. This lipid free radical may further react with molecular oxygen to form the lipid peroxyl radical. Peroxyl radicals can react with fatty acids to produce lipid free radicals, thus propagating the reaction (Thiele and Elsner, 2001). One of the byproducts of lipid peroxidation is malondialdehyde. The product can cause damage to cell membrane or DNA leading to cytotoxicity, mutagenecity or cell death (Cross CL *et al*, 1987).

DNA DAMAGE

Oxidative stress in the form of DNA damage is known to be a major factor in skin hyperpigmentation. Three unrelated sources of genotoxic stress is in skin are reactive oxygen species (ROS), reactive carbonyl species (RCS) and sunlight. Sunlight is the major source of skin damage as it leads to DNA damage directly via formation of pyrimidine dimers and other photoproducts (Ullrich, 2002) and indirectly via generation of ROS and RCS by photooxidation and photosensitization reactions (Wondrak, Cervantes-Laurean *et al*, 2002; Roberts, Wondrak *et al*, 2003). While UVB responsible for

most of the direct DNA damage by sunlight, is the most effective at initiation of skin hyperpigmentation. Recent studies have shown that UVA rays that induce ROS also cause hyperpigmentation formation. In addition to DNA, proteins also are targets for damage by ROS in skin. Carbonyl stress, mediated by RCS from metabolic sources , lipid peroxidation and glycoxidation targets skin cell DNA and extracellular matrix protein with accumulation of proteins advanced glycation end products (AGE) during chronological and actinic aging of skin (Wondrak GT *et al,* 2002; Roberts MJ *et al*, 2003). Recently AGEs have been identified as potent UVA sensitizers of photoxidative stress in human skin, establishing a vicious cycle of RCS and ROS formation in sunlight induced genotoxic stress.

IMMUNOLOGICAL EFFECTS

While the mechanisms of photoimmune suppression are still poorly understood, DNA damage is a major factor leading to reduced immune surveillance (Ullrich SE, 2002). Two major cell targets are Langerhans cell where DNA damage leads to suppression of cell migration and antigen presentation functions and keratinocytes where DNA damage results in altered cytokine signaling and reduced immune function potentially involved in generation of T suppressor cells (Cruz PD *et al*, 1990). In addition to DNA, two other targets have been identified for immuno suppression. The photoconversion of urocanic acid to cis-urocanic acid has been implicated in immune suppression (Moodycliffe AM *et al*, 1993), also ROS generation including membrane lipid peroxidation has been implicated in immune suppression (Ullrich SE,2002), possibly by altering signaling pathways at the membrane level, although DNA as the ultimate target is still a possibility.

CONCLUSION

Skin, the largest human body organ, provides a major interface between the environment and the body and is constantly exposed to an array of chemical and physical environmental pollutants (Athar M, 2002). Although the skin possess an elaborate antioxidant system to deal with the UV-induced oxidative stress, extensive and chronic exposure to UV can exceed the cutaneous antioxidant capacity, leading to oxidative damage that may result in skin hyperpigmentation ,immunosuppression and premature skin aging(Katiyar SK and Elmets CA, 2001)

One approach to protect human from the harmful effects of UV irradiation is to use active photoprotectives. In recent years, naturally occurring compounds have gained considerable attention as protective agents. Vitamin C, E and β- carotene have been incorporated into many skin care products for instance. Another approach is afforded by the antioxidant properties of phenolics. These substances can be used as ingredients in human diet or added to preparations for topical application (Tebbe B, 2001; Afaq F *et al*, 2002).

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