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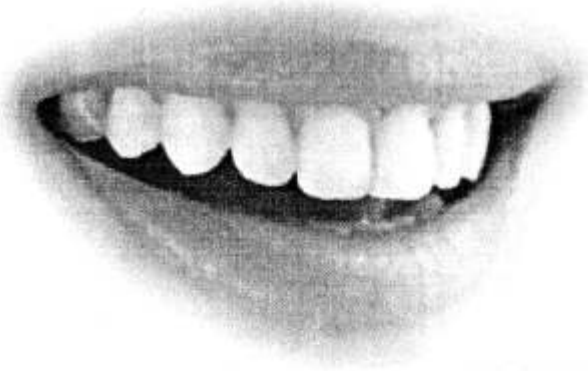

It is a curve
that sets everything straight.

-Phyllis Diller

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IN THIS ISSUE ....

"OXIDATIVE STRESS AND ORAL LICHEN PLANUS : A Possible Association?"

Dr Nisheeth Anshumalee*, Dr MC Shashikanth**, Dr Swati Sharma***

Abstract

After many years of controversies and being dismissed as non-existent in biological systems or simply an unimportant curiosity, free radicals, have become accepted into biochemical and medical orthodoxy and their existence and importance in living systems is now widely accepted. The role of oxidative stress in various pathologic processes including inflammation and carcinogenesis is being studied and antioxidants are being widely used in the management of various diseases including many oral mucosal diseases. Oral lichen planus, a chronic inflammatory disease affecting the oral mucosa is one such condition. The role of oxidative stress in the pathogenesis of OLP is not established as such, but many recent studies are pointing towards this possibility and are hence paving way for the new management modalities using antioxidants for this condition.

This review article tries to throw a light on such possible association between lichen planus and oxidative stress.

KEY WORDS : Lichen planus, Oxidative stress, Free radicals, Antioxidants, Lycopene.

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INTRODUCTION

After many years of controversies and being dismissed as non-existent in biological systems or simply an unimportant curiosity, free radicals, have become accepted into biochemical and medical orthodoxy and their existence and importance in living systems is now widely accepted.[1,2]

A free radical can be **defined** as "a chemical species possessing an unpaired electron". As such, free radicals can be formed in three ways:

1. By the homolytic cleavage of a covalent bond of a normal molecule with each fragment retaining one of the paired electrons
2. By loss of a single electron from a molecule
3. By addition of a single electron to a molecule (Electron transfer)

The electron transfer is a far more common process in biological systems than homolytic fission.

The most important free radicals in the biological systems are radical derivatives of oxygen, which include superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and ($^{\bullet}OH$), hydroxyl radical.

Superoxide is formed by the transfer of a single electron to oxygen molecule, while, transfer of two electrons produces H_2O_2, which is also formed by the reaction of two superoxide molecules. H_2O_2 is not a free radical but falls in the category of reactive oxygen species (ROS) and in the presence of transient metal ions breaks down to produce most reactive and damaging hydroxyl radical ($^{\bullet}OH$), which is also generated by reaction of H_2O_2 with superoxide. Hydroxyl radical is extremely reactive and reacts with most biomolecules and causes considerable damage within a small radius of its site of production.

Superoxide is not particularly damaging, but its main significance is probably as a source of H_2O_2 and reaction with nitric oxide (NO), a physiologically important biomolecule. At low pH it forms perhydroxyl radical ($HO_2^{\bullet}$). Singlet oxygen is another ROS, which can lead to and is generated by free radical reactions.

Other free radicals are carbon centered radicals ($R^{\bullet}$) that are generated from attack of an oxidizing radical on a biomolecule such as lipid, nucleic acid, carbohydrate or protein, and react very rapidly with oxygen to produce peroxyl radical ($ROO^{\bullet}$), which can generate alkoxyl radicals ($RO^{\bullet}$). Sulphur atoms can also be the centre of free radicals ($RS^{\bullet}$).[1]

PRODUCTION OF FREE RADICALS IN CELLS

With the exception of unusual circumstances such as influence of ionizing radiations, free radicals are generally produced in cells by electron transfer reactions. These can be enzyme or non enzyme mediated, and their production can be either accidental or deliberate. Activated phagocytes deliberately generate superoxide as a part of their bactericidal activity, which may leak or diffuse away from their site of production and cause damage to other biomolecules.

Under normal circumstances, the major source of free radicals in cells is electron leakage from electron transport chain.

Another source of superoxide in animal cells is the autoxidation of certain compounds such as ascorbic acid, thiols, adrenaline and flavin co-enzymes, and their reactions are greatly enhanced by involvement of transient metal ions.[3]

DAMAGING REACTION OF FREE RADICALS

All the major classes of biomolecules may be attacked by free radical, but lipids are probably the most susceptible and cell membranes are a rich source of same being composed mainly of polyunsaturated fatty acids (PUFA). This destruction is known as lipid peroxidation and leads to generation of a fatty acid radical ($L^{\bullet}$), which reacts with oxygen to form a fatty acid peroxyl radical ($LOO^{\bullet}$) and aldehydes that oxidize further PUFA molecules. These reactions often involve transitional metal ions. The aldehydes formed can diffuse away from original site of production to damage other cell organelles.

Proteins and nucleic acids appear less susceptible than PUFA to free radical attacks. Random attacks on proteins are less likely to be very damaging unless extensive, allowed to accumulate or the damage occurs at a particular important site (site specific damage). DNA is readily attacked and damaged by the oxidizing radicals being generated in their vicinity.[1]

DEFENCES AGAINST FREE RADICALS

Because some free radical production in animal cells is inevitable and because they can be very damaging, defenses against the deleterious actions of free radicals have evolved. These are known as **antioxidant defenses** and are of four main categories:

1. Those who prevent the generation of free radicals
2. Those who intercept any that are generated.
3. Those who repair the cellular damage already done.
4. Antioxidant drugs.

The **preventive** defences include efficiency of electron transfer, sequestration of transitional metal ions, and removal of peroxides. Enzymes like catalase and glutathione peroxidase decompose peroxides.

The **interceptive** defences are "scavenging" of free radicals by enzymes such as superoxide dismutase and non enzymatic substance like á-tocopherol, an important "chain breaking" antioxidant, which intercepts lipid peroxyl radicals to terminate lipid peroxidation, and ubiquinol. Other important antioxidants are ascorbic acid in both within and outside the cell, uric acid in plasma, and glutathione in cell cytosol.

A third category of natural antioxidant defences are **repair processes**, which remove damaged biomolecules before they can accumulate and before their presence results in altered cell metabolism or viability.[1] **Antioxidant drugs** are being developed, studied and being used widely for treatment or prevention of free radical mediated tissue damages.

FREE RADICALS AND INFLAMMATION

Although the free radicals have the capacity to mediate tissue destruction, they play a role in a variety of normal regulatory systems, the deregulation of which may play an important role in inflammation.

Neutrophils, eosinophils and mononuclear phagocytes possess a membrane bound cytochrome-b-245 NADPH oxidase system, which

gets activated by increased consumption of oxygen by these cells during microbial phagocytosis (Respiratory burst), and leads to increased NADPH production via HMP shunt pathway, and generation of $O_2^{\bullet}-$, H_2O_2, $^{\bullet}OH$, hypochlorus acid (HOCl) and ROS, which are capable of damaging cell membranes and a wide variety of biomolecules.

'Free' iron (transition metal ion) is not present in biological systems but exists in a complex form. The low pH generated locally during inflammation may contribute to iron decompartmentalisation and availability of transition metal ions.[4]

Additionally, the radical NO has been shown to be an important cytotoxic effector molecule in defence against tumor cells, parasitic fungi, protozoa, helminths and mycobacteria. NO is relatively unstable in aerobic conditions and is generated by enzyme NO synthase. It is a potent vasodialator, thus contributing considerably to cardinal signs of inflammation.

The genes like *c-fos, c-myc ,c-jun* and *â-actin* that encode transcription factors responsible for the induction of cell growth, differentiation and development, are induced rapidly by ROS, possibly through DNA strand breaks. Thus low doses of ROS can stimulate the growth of fibroblasts and epithelial cells promoting fibrosis and wound healing. In carcinogenesis and inflammatory disorders, overproduction of radicals may cause the excessive proliferation of tissues.

Free radicals have been implicated in the activation of NFêB, an important transcription factor in inflammatory systems controlling the transcription of a number of cytokine genes including IL-2 and TNF-á, as well as MHC Class 1 gene and IL-2 receptor gene.

Formation of Schiff base (R–CH=N–Rc, a condensation product of aldehydes and ketones with primary amine) between ligands on antigen presenting cells (APCs) and T- cells is essential for antigen induced T cell activation, and prevention of same by addition of low concentrations amines or aldehydes (products of lipid peroxidation) inhibits recognition of antigens by T cells but not antigen uptake or processing by APCs. Oxidative mitogenesis, also dependent on Schiff base formation, results in a vigorous proliferative T cell response.

DNA damages like single or double strand breaks by free radicals may also account for the DNA autoantibodies seen in various conditions like systemic lupus erythematosus. Also, the HSPs are shown to be upregulated by various physiologic stressors including free radicals and inflammatory mediators.[2]

FREE RADICALS AND ANTIOXIDANTS IN OLP

Lichen planus being a chronic inflammatory disease, the role and importance of free radicals in the pathogenesis of LP is being studied and debated since last few years.

Carotenoids are known to have antioxidant properties, and Rollman O and Vahlaquist A et al in their study found lower levels of serum carotenoids in LP patients (84.9 ± 33.5) as compared to healthy controls (108.2 ± 43.7), however this difference was statistically not significant.[3]

Oxidative stress has been implicated in the pathogenesis of lichen sclerosus (LS), a chronic inflammatory disorder affecting genitalia that shares clinical features with erosive LP of vulva.[4] A significant increase in lipid peroxidation products was found in vulval LS tissue specimen particularly within basal cell layers, which also showed increased oxidative DNA damage, increased protein oxidation and disturbed enzymatic antioxidant defences.[5]

Bernanan PA et al studied 30 cases of OLP and 10 normal buccal mucosal biopsies for increased expression of inducible NO synthase (iNOS) expression. iNOS expression was not noted in normal mucosa and 21 cases of OLP, but was noted in less than 5 % cell in 9 cases of OLP. The authors stated that this reduced expression of iNOS might be due to use of formalin fixed tissues which resulted in false negative results, or the antibodies used were not able to detect low levels of expression. Also, many cytokines including IL-2, IL-4, IL-10, TGF-â and TNF-á are reported in OLP, and IL-4, IL-10 and TGF- â are known to inhibit induction of iNOS. Further p53 gene is known to downregulate iNOS expression, and high levels of p53 have been reported in OLP. These two factors too could have been responsible for low iNOS expression.[6]

There are no reported studies investigating involvement of oxidative stress and antioxidant enzyme expression in OLP patients. However, a study done on erosive vulval LP cases showed increased oxidative stress and decreased antioxidant enzyme expression in biopsy specimens, thus elucidating a role of free radicals in pathogenesis of LP. The expressions of antioxidant enzymes copper zinc superoxide dismutase (CuZnSOD), manganese SOD, and catalase were significantly decreased in epidermal layers. A significant increase of lipid peroxidation products and oxidative DNA damage was found within the epidermis. Protein oxidation was found to occur predominantly in the papillary dermis.[6]

Nagao T et al studied the levels of serum antioxidant micronutrients in OLP patients and healthy controls. No significant differences were noted in carotenoid levels examined, except for a significantly lower level of lycopene found in the erosive and atrophic OLP cases. Though, they attributed this to be an incidental finding or related to less intake of lycopene rich food due to presence of symptoms, the role of lower levels of this antioxidant in the causation of this disease process can not be ruled out completely without evidences from further studies.[7]

In a double blind, randomized, placebo controlled study, lycopene, a potent antioxidant was found effective in the management of OLP as it produced statistically significant reduction in both the signs and symptoms of the disease. Two groups of 15 symptomatic OLP patients each, when treated with 8mg/day of lycopene or an identical placebo for eight weeks, showed a significantly better overall treatment response in lycopene group with 11 patients (73.3%) showing a complete cure (70-100% relief), and all 15 showing partial or complete (50-100%) relief, in contrast in placebo group only 4 (26.4%) showed complete cure and 10 (66.7%) partial to complete cure.[8]

These therapeutic effects of a potent antioxidant like lycopene also indirectly substantiate the hypothesis of the role of oxidative stress in the pathogenesis of LP.

CONCLUSION

Thus we see that there are evidences and chances, though not well supported by many studies, of free radicals being involved in the pathogenesis of OLP, and hence this area needs further research.

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