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Reactive Oxygen Species and Its Implications in Periodontal Disease

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Abstract

Periodontitis is a chronic inflammatory disease due to complex interactions between periodontopathogens and the host immune response. Prognosis of periodontal disease is dependant on the host immune response and susceptibility. The activation of immune system and the production of oxygen free radicals and their related metabolisms are two important interrelated factors involved in the prognosis of periodontal diseases. Free radical/Reactive oxygen species are essential for many natural biological processes and low doses of certain radicals or radical derived species can stimulate the growth of fibroblasts and epithelial cells in culture and imbalance can cause tissue damage. The relationship between Reactive oxygen species and its effect on periodontal tissues are discussed here

Keywords: Periodontitis-Reactive Oxygen Species-Antioxidants-Neutrophil aspects

Introduction

Periodontitis is a complex interaction between pathogens and host immune response with two important pathophysiology, activation of immune system and production of oxygen free radicals. Reactive oxygen species are highly reactive and diverse species, capable of extracting electrons and thereby oxidising a variety of biomolecules, vital to the cell and tissue function, which not only include oxygen free radicals, but also nitrogen and chlorine species. It also contains other reactive species which are not true radicals but are nevertheless capable of radical formation in the intra and extra cellular environment. Radicals can react with other molecules in severalways. When two radicals meet, they can combine their unpaired electrons and join to form a covalent bond. A radical might donate its unpaired electron to another molecule or it might capture an outer orbital electron from another molecule in order to pair, thus inducing the other molecules to turn into free radicals. Reactive oxygen species are produced continuously in humans in physiological and pathological conditions. The production of oxygen free radicals contributes to oxidative stress induced diseases. The term Reactive Oxygen Species includes not only oxygen free radicals, but also non

radical derivatives involved in oxygen radical production. The most biologically important free radical system is a derivative of oxygen.

Free radicals are defined as any species capable of independent existence that contain one or more unpaired electron. Free radicals can be positively or negatively charged or electrically neutral. The most important free radicals species involved in inflammatory injuries to tissue are hydroxyl radicals, the superoxide anion, the nitric oxide radical, the hydrogen peroxide radical, the hypochlorous acid and singlet oxygen which are the reactive oxygen species.

Invitro study by Sheikk et al 2007, showed that Fusobacterium nucleatum, a periodontal pathogenic gram-negative bacterium, was able to stimulate Reactive Oxygen Species induced Lipid peroxidation. Abnormal reactive oxygen species production can lead to physiological and pathological consequences of hypoxia, impairment of aerobic factors, lysis of cell membrane, DNA fragmentation, ischemic injury, activation of proteolytic enzymes, inactivation of proteolytic enzyme inhibitors and more drastically, cell death. In periodontium, Reactive Oxygen Species causes collagenolysis and degradation of specific extracellular matrix components such as hyaluronic acid and proteoglycans. There are various mechanisms to prevent Reactive Oxygen Species damage by enzymatic and non-enzymatic methods.

Redox State-Chapple 2007[1]

In normal physiology, the dynamic equilibrium between Reactive Oxygen Species and Antioxidants is maintained. When this equilibrium shifts in the favour of Reactive Oxygen Species, either by reduction in antioxidant defence or because of increase in Reactive Oxygen Species production or action, which results in oxidative stress[2].

Formation of Reactive Oxygen Species

The addition of one electron to oxygen results in the formation of superoxide anion.

$O_2 + e^- \longrightarrow O_2^{\cdot -}$

The addition of second electron results in the formation of hydrogen peroxide. (H_2O_2)

$O_2 + e^- + 2H^+ \longrightarrow H_2O_2$

The addition of the third electron results in the formation of hydroxyl radical ($^{\cdot}OH$)

$H_2O_2 + e^- \longrightarrow OH + OH^-$

The addition of the fourth electron results in the formation of water (H_2O)

$^{\cdot}OH + e^- + H^+ \longrightarrow H_2O$

Sources of Reactive Oxygen Species

Exogenous sources are Heat, Trauma, UVLight, Ozone, Smoking, Exhaust fumes, Infection, Excessive exercise and certain Therapeutic drugs. Endogenous sources are by-products of metabolic pathways and functional generation by host cells (Phagocytes) and cells of the connective tissue (Osteoclasts andFibroblasts).

Oxidative Stress

It was defined by Sies as a disturbance in the pro- oxidant-antioxidant balance in favour of the former, leading to potential damage due to its increase in Reactive Oxygen species production or action.[3]Moderate oxidation may trigger apoptosis while more intense stress may cause necrosis. In humans, oxidative stress is thought to be involved in development of many disease or may aggravate their symptoms. This includes Cancer, Atherosclerosis, Myocardial infarction, Bipolar disorder, Fragile X Syndrome, Sickle cell disease, Chronic fatigueSyndrome and Periodontitis.

Redox Potential

It is the measure of the affinity of a substance for electrons relative to hydrogen. Substances more strongly electronegative than hydrogen have positive redox

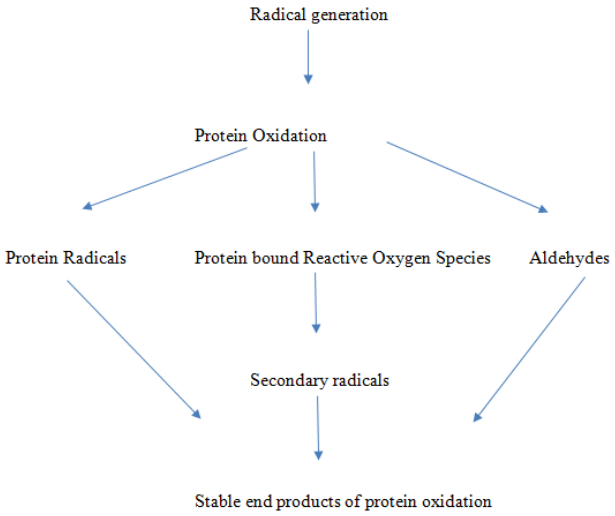
potential and are oxidants. (i.e. They are capable of oxidising hydrogen). Substances which are less electronegative than hydrogen (i.e.capable of reducing hydrogen) have negative redox potential. Oxidation and reduction reactions always go together and are termed as redox reactions. Low redox potential within the gingival crevice and the periodontal pocket is required for the growth and survival of the sub gingival anaerobes. But within the cells and tissue, low redox potential is protective against oxidative stress. Bacteria are not intracellular pathogens and hence maintaining a low redox state within the cell may not have relevance to the high redox states within the periodontal pockets or gingival crevice.

Mechanisms

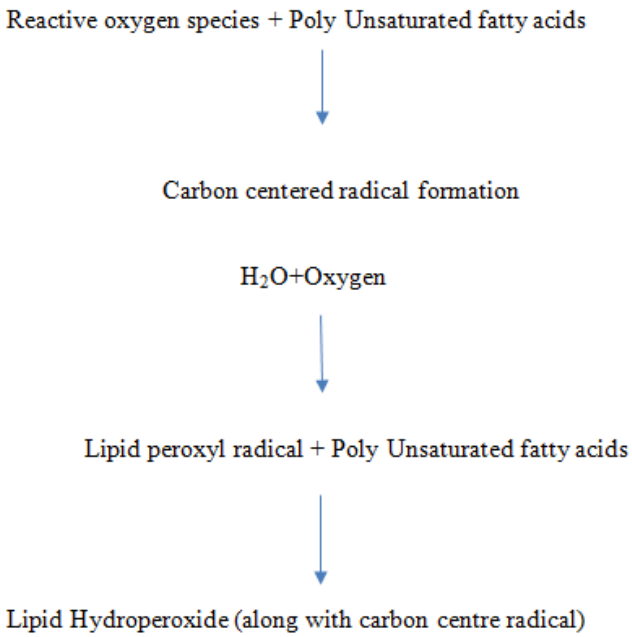
Reactive Oxygen Species cause tissue damage by a variety ofmechanisms like protein damage, lipid peroxidation, DNA damage, oxidation of important enzymes, stimulation of the proinflammatory cytokines release etc.

Protein Damage:[4]

Effect of Reactive oxygen species on proteins and amino acids are



Lipid Peroxidation



Three main markers of lipid peroxidation are Thiobarbituric acid reactive substances, Malonaldehyde and Isoprostanes. Lipid peroxidation can be estimated by analysing the exhaledair or oral cavity is sampled for volatile hydrocarbons.

DNA Damage

Mechanism of DNA damage by peroxynitrite and hydroxy radicals include[5]

-Strand Breaks

-Base pair mutations (purine and pyrimidine bases)

-Conversion of guanine to 5 hydroxy guanine

-Deletions

-Insertion

-Nicking

-Sequence of Duplications

Evidence for the presence and role of Reactive oxygen species is discussed by Halliwell[6]. Reactive oxygen species can be key mediators of tissue injury in a given disease and described in advance by Halliwell and termed has Halliwell's postulates. Four Criteria were proposed by him. Halliwell's postulateshave an underlying assumption

that Reactive oxygen species are generated at a level that results in direct damage to tissue components

Halliwell's Postulates

The four criteria proposed by Halliwell are

- Reactive oxygen species or the oxidative damage caused must be at the site of injury
- The time course of reactive oxygen species formation or the oxidative damage caused should occur before or at the same time as tissue injury
- Direct application of reactive oxygen species over a relevant time course to a tissue at concentrations found in vivo should reproduce the damage similar to that observed in the diseased tissue
- Removing or inhibiting reactive oxygen species should decrease the tissue damage to an extent related to their antioxidant action in vivo

  Neutrophils have the ability to withstand the hostile environment in the redox potential and are able to function and initiate respiratory burst activity in the presence of sulphide at the toxic levels formed at the diseased state and forms reactive oxygen species .Reactive oxygen species generation in neutrophils require minimal oxygen tension above 1.1 and pH of 7.0-7.5. Both the conditions are present in the Periodontal pocket, indicating that chronic and excess reactive oxygen species production results in periodontal tissue damage[7]. Low density lipoproteins are oxidised products produced locally by neutrophil Reactive oxygen species which will further amplify the neutrophil reactive oxygen species. Increased oxidative load may be due to delay in the neutrophil to transit the tissue effectively.

Methodological Aspects of Reactive Oxygen Species Generation by Neutrophil

Luminol dependant Chemiluminescence:

Luminol has the capacity to cross cell membrane. The total reactive oxygen species generation is detected by using Luminol dependant chemiluminescence. Isoluminol cannot cross the cell membrane and it is more hydrophilic. It is similar to Luminol chemiluminescence substrate which is used to detect the extracellular reactive oxygen species generation.

Methods To Detect Reactive Oxygen Species

1.Spin trap technique

2.Allantoin- as a marker of oxidative stress in human erythrocytes

3.Air sampling in oral cavity

4.Biomarkers

Role of Reactive Oxygen Species on Periodontal Tissues and Components

- Reactive oxygen species produced by phagocytes has been associated with the defence of the body to infection[8]
- Reactive oxygen species at high levels are chronically produced can cause oxidative stress within tissues and result in direct damage to cells and the extracellular matrix.
- Gingival fibroblast and epithelial cells when exposed to unstimulated neutrophils from medically and periodontally healthy subjects experience minimal detachment or damage. [9,10]
- Certain reactive oxygen species (superoxide and hydrogen peroxide) activate osteoclast and promote osteoclast formation
- Osteoclasts produce reactive oxygen species at the ruffle border- bone interface, suggesting a more direct role in resorption
- Reactive oxygen species at physiological levels can selectively damage proteoglycan associate with both the supporting periodontal tissue and alveolar bone.[11]

- Increased local breakdown of collagen in periodontal disease has been suggested from investigating GCF for collagen metabolites. [12]

Conclusion

Oxidative stress lies at the heart of the periodontal tissue damage that results from host microbial interactions, either as a direct result of excess Reactive oxygen species activity or indirectly as a result of the activation of redox sensitive transcription factors and creation of pro inflammatory states. The resolution of inflammation is a natural step in the inflammatory process, that leads to the concept that tissue injury mediated by inflammation is a consequence of the inability of the host to resolve the inflammation, not the initial inflammation itself. Inflammation is necessary to protect the host from infection, but persistent inflammation can also cause disease. Hence resolution of inflammation in a timely fashion will protect the host from tissue injury, while the infectious agent is still cleared.The use of some antioxidants has the potential to improve periodontal clinical parameters in the field of preventive periodontics.[13]

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