ROLE OF REACTIVE OXYGEN SPECIES IN PERIODONTITIS: A REVIEW ARTICLE

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ABSTRACT

Many epidemiological studies have shown that more than two third of world's population suffers from periodontal disease. Polymicrobial complex is found to be the primary etiological agent for this inflammatory disease. This polymicrobial complex is found in plaque. Periodontitis begins from adherence of plaque to the tooth surface. Polymicrobial complex is predominantly composed of Gram –ve anaerobic or facultative bacteria. The dental plaque which is responsible for periodontitis is located in sub-gingival area which extends to tooth apices causing inflammation of periodontal tissue. The most identified bacteria species found in development of periodontitis are P.Gingivalis, P.Intermedia , Actinomyces Viscous, Bacteroids forsythus, Campylobacter Rectus, Treponema denticola and Fusobacterium nucleatum. Apart from this periodontitis is also caused by environmental risk factors, genetic disorders and systemic factors. Studies show that people suffering from Diabetes Mellitus, smokers suffer from periodontitis. The bacterial species found in dental plaque initiate the production of cytokines such as Interleukin-8 and TNF-α which further causes increased number and increased activity of polymorphoneuclear cells (PMN) along with these cytokines. PMNs also produce Reactive Oxygen Species (ROS), Superoxide via respiratory burst mechanism as a part of defence response to infection. Just like interleukins ROS have deleterious effect on tissues if they are produced in excess. Human body counters the harmful effects of ROS by its own defence mechanism to eliminate from body. This review aims to focus on the role of ROS, free radicals and anti-oxidants in pathophysiology of periodontal diseases

Keywords: Periodontal disease, PMN, ROS.

INTRODUCTION:

Periodontitis is an infectious, inflammatory disease of periodontal tissue associated with specific bacteria characterised by inflammation of supporting tissues of teeth and progressive destruction of alveolar bone structure (Bone loss) and connective tissue around the tooth. Periodontitis is the continuation of previously suffered gingivitis. Three types of periodontitis are found to be very common in human population are Chronic periodontitis, Aggressive periodontitis and Necrotising ulcerative periodontitis. The progression of

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destructive disease is supposed to be dependent on an abnormal host response to subgingival plaque biofilm. Over the past few years strong evidences are found to implicate oxidative stress in pathogenesis of Periodontitis. Free radicals and reactive oxygen species (ROS) are essential to many biological processes. These free radicals and ROS stimulate the growth of fibroblasts and epithelial cells if produced in low concentrations. But at higher concentrations these free radicals and ROS may result in tissue injury.

Dental plaque harbors a number of bacterial pathogens. Most common identified pathogens in periodontitis are especially gram–ive stem bacteria including Porphyromonas gingivalis, Prevotella intermedia, Actinomyces viscous , Bacteroid forsythus, campylobacter rectus, Treponema denticola and Fusobacterium nucleatum. These bacterial pathogens stimulate host cells to release various interleukins and TNF-α . These pro-inflammatory cytokines attract poly morphoneuclear cells (PMNs) to the site of infection. PMN encounters the bacterial challenge by producing proteolytic enzymes and oxygen by oxidative burst. The human body has developed an antioxidant defence system comprising endogenous antioxidants such as Vit A , Vit C, Vit E and B, carotene and enzymatic oxidants such as superoxide dismutase, catalase and nucleoperoxide. This antioxidant system functions to detoxify ROS. PMNs, neutrophils and macrophages produce ROS which are released in extracellular environment. The ROS does not have specific target so that it can cause tissue damage with DNA damage, lipid peroxidation, protein oxidation of other important enzymes and stimulation of the release of pro-inflammatory cytokines by monocytes and macrophges.

DISCUSSION:

Chronic periodontitis is a chronic inflammatory disease of a complex etiology. The primary etiology is bacteria found in dental plaque biofilm and is exacerbated by various factors. In this case excess production of reactive oxygen species and changes in state can lead to abnormal activation of apoptosis approaches important factors involved in production of various clinical features of periodontitis and periodontitis extensions. Several studies have demonstrated a role of reactive oxygen species (ROS) in the deregulation of apoptosis. Neo-epitopes are produced between ROS and body which then stimulates a broad spectrum which are associated with tissue damage and breakdown of periodontium. Many studies

in periodontitis patients have shown oxidative stress in pathogenesis of disease.

Mechanism of tissue damage

Mechanism of protein damage	**Mechanism of lipid damage**	**Mechanism of DNA damage**
The effects of ROS on proteins include	Products of lipid per-oxidation include a variety of bioactive molecules	Mechanism of DNA damage by peroxynitrite & hydroxyl radicals
include		
Protein folding/unfolding	Conjugated dienes	Strand Breaks
Protein fragmentation	Lipid peroxides	Base pair mutations
Protease degradation of the modified protein	Aldehydes e.g.malondialdehyde	Conversion of guanine to 8-hydroxyguanine
formation of protein radicals,protein bound ROS	Acrolein	Deletions
formation of stable end products. e.g. carbonyl compounds such as oxo-acids or aldehydes (e.g. alanine to acetaldehyde)	Isoprostanes e.g.F2-isoprostanes	Insertions
	Neuroprostanes (F4-Isoprostanes)	Nicking
	Volatile hydrocarbons,e.g. pentane,ethane	
	Volatile hydrocarbons,e.g. pentane,ethane	

Origin of Reactive Oxygen Species & Free Radicals

It is well known that free radicals & ROS are essential for many biologic process. They are produced as superoxide ions by neutrophils at the site of infection. Free radicals are defined as any species capable of independent existence that contains one or more unpaired electrons. By nature they are highly reactive and diverse species capable of extracting electrons thereby oxidizing a variety of bio-molecules vital to cell and tissue functions, which not only include oxygen free radicals but also chlorine and nitrogen species. ROS term has become more popular because it encompasses other reactive species which are not true radicals but are nevertheless capable of radical formation in the intra and extracellular environments. True free radicals include Superoxide hydroxyl($O_2^{\cdot -}$), Perhydroxyl ($HO_2^{\cdot -}$), Hydroperoxyl ((HOO$^{\cdot}$), Alkoxyl(RO$^{\cdot}$), Aryloxyl (ArO$^{\cdot}$), Arylperoxyl(ArOO$^{\cdot}$), Peroxyl (ROO$^{\cdot -}$), Acycloxyl(RCOO$^{\cdot}$), and Acylperoxyl(RCOOO$^{\cdot}$), where as ROS includes hydrogen peroxide (H_2O2), Hypochlorus acid (HOCL), Singlet oxygen ($^1O_2$), and Ozone (O_3).

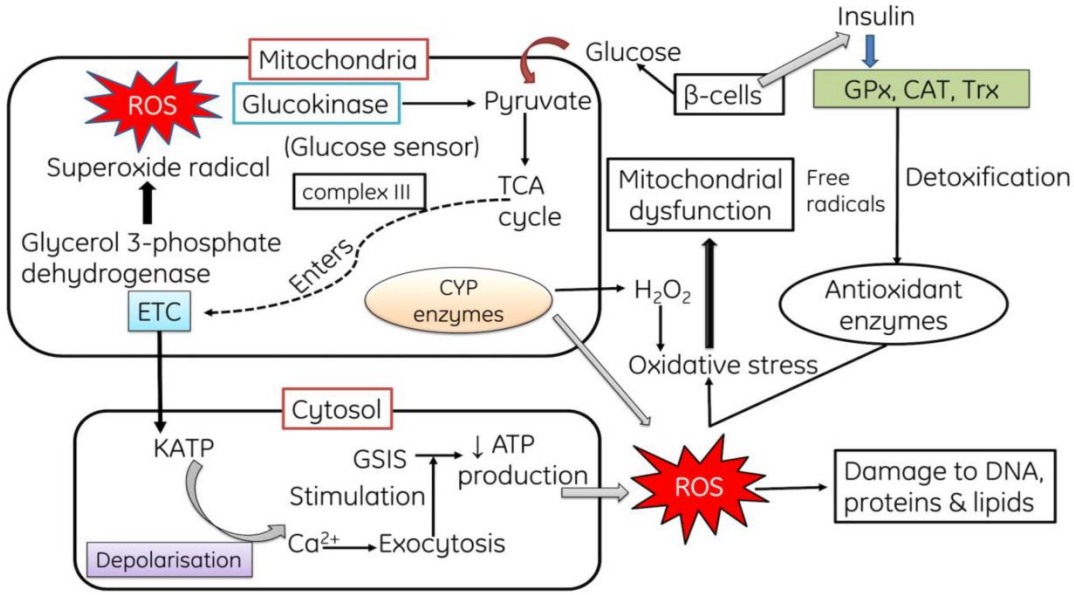

Fig 1: The mechanism for the formation of oxidative stress

Role of ROS in the Pathogenesis of Periodontitis

Periodontal disease can be caused by an immune reaction which takes place between the pathogen and and host. Sub-gingival plaque is the main etiological factor for inflammation in periodontal tissue. Lipopolysaccharides (LPS) and DNA from these bacteria activates the Protein-1 pathway & the factor-kβ pathway in gingival fibroblasts via CD14 and TLR-4 (Toll like receptors) and the production of inflammatory cytokines.

Bacterial cell components and inflammatory cytokines cause activation of polymorphoneuclear cells and accelerates the production of ROS. At the same time activation of NF-kβ and AP-1, causes osteoclast activation and increases matrixmetaloproteinase concentration which ultimately results in tissue damage. Periodontal tissue damage results in the production of excess lipid peroxide, inflammatory mediators and oxidized proteins. These products further activates macrophages , neutrophils and fibroblasts to produce more Reactive Oxygen Species(ROS). All these sequences make a related circle among Periodontal pathogens, ROS and Tissue damage. ROS can directly damage gingival cells. ROS generated from neutrophil myeloperoxidase, chloride, glucose and glucose oxidase causes lysis of epithelial targets which can be inhibited by azide and catalase. Neutrophils in periodontitis show a reactive phenotype with respect to ROS production.

Certain ROS like superoxide and hydrogen peroxide activates osteoclasts and cause proliferation of osteoclast formation. Osteoclasts themselves can produce ROS when they ruffle bone borders which suggest its direct role in bone resorption. In vitro study proteoglycans of alveolar bone degrades hydroxyl radicals and hydrogen peroxide. ROS effects on proteoglycans and glycosaminoglycans can damage soft tissue and periodontium. This degrades core protein and glycosaminoglycan chains. Many evidences suggest that ROS in low levels can selectively destroy proteoglycans with periodontal soft tissue and alveolar bone.

Collagen structure which has high content of proline and hydroxyproline content is highly succeptible to damage by ROS. Hydroxyl radicals and superoxide anions can rotate collagen into small peptides in proline and hydroxyl proline residue, thus freeing peptides containing hydroxyl proline. Collagen and serum proteins are indirectly modified by ROS through interaction with lipid peroxidation. Products such as malondialdehyde, can significantly alter fibroblast function such as adhesion , proliferation and longevity. Changes such as in vivo fibroblast function occurs in periodontal disease due to increased lipid peroxide in gingival tissue. Oxidative changes in collagen in the periodontal connective tissue can inhibit the migration of neutrophils through the tissues and increases the potential to produce ROS. Superoxide can modify chloroform factor bound to serum plasma albumin. Metalloproteinase imbalance also occur in the fluid of gingival groove and in the prtiodontal tissue.

The α1-antitrypsin enzyme plays role of neutralizing the lysosomal collagenase and elastase enzymein phagocytosis. The oxidation of α1-antitrypsin causes a loss of inhibitory role in protease and proteolytic fermentation of chymotrypsin, rennin, kallikerin, plasmin, urokinase, thrombin, elastane and collagenase. Activation of the transcription factor N-F-Kb-ROS is induced by the release of bacterial lipopolysaccharides, IL-1 and TNF-α, NF-kB diffuses from the cytoplasm and binds to the promoter so that it can stimulate structural m-RNA transcription genes for pro-inflammatory cytokines.

MMP is the neutrophil MMP-8(Collagenase-2) and MMP-9(Gelatinase-B). MMP decreases in collagen , while MMP-9 is a gelatinolytic enzyme. This gelatinolytic enzyme degrades extracellular matrix proteins including collagen type IV and membrane proteins. Both types of matrix metalloproteinases are present in the gingival and salivary fluids that reduce collagen , specially during the

inflammatory process in people with gingivitis and periodontitis. This enzyme stimulates fibroblasts and macrophages to produce neutral metalloprotease procollagenase. Fibroblasts mainly produce MMP-1, MMP-13, MMP-2 (gelatinase-2) MMP-3 and MMP-14.

CONCLUSION:

Oxidative stress lays at the heart of the periodontal tissue damage that results from host microbial interactions. During infection immune system produces ROS which are released in to the extracellular environment. The tissue damage is a result of excessive ROS activity / antioxidant deficiency or as a result of activation of redox-sensitive transcription factors and positive creation of pro inflammatory stake. ROS does not have a specific target that could damage tissue specially in periodontitis.

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