

Review article

# Reactive oxygen species and antioxidants in inflammatory diseases

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**Abstract.** This paper aims to review the rôle of free radical-induced tissue damage and antioxidant defence mechanisms in inflammatory diseases that involve pathogenic processes similar to the periodontal diseases. There is a clearly defined and substantial rôle for free radicals or reactive oxygen species (ROS) in periodontitis, but little research has been performed in this area. This paper reviews the considerable data available relating ROS activity and antioxidant defence to inflammatory diseases and attempts to draw parallels with periodontitis, in an effort to stimulate more periodontal research in this important area. The recent discovery of the transcription factor nuclear factor  $\kappa$ B (NF- $\kappa$ B) is reviewed and several potential pathways for cytokine-induced periodontal tissue damage, mediated by NF- $\kappa$ B, are discussed. Emphasis is placed on cytokines that have been studied in periodontitis, principally TNF- $\alpha$ , IL-1, IL-6, IL-8 and  $\beta$ -interferon. The link between cellular production of such important mediators of inflammation and the antioxidant (AO) thiols, cysteine and reduced glutathione (GSH), is discussed and it is hypothesised that NF- $\kappa$ B antagonists may offer important therapeutic benefits.

Key words: free radicals; antioxidants; reactive-oxygen species; periodontitis; thiols; neutrophils; glutathione; NF- $\kappa$ B; review

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The human periodontal diseases are inflammatory disorders that give rise to tissue damage and loss, as a result of the complex interactions between pathogenic bacteria and the host's immune response. It is likely that the role of reactive oxygen species is common to both bacterial and host-mediated pathways of tissue damage. Free radical species have been implicated in the pathogenesis of over 100 conditions (Halliwell et al. 1992) including rheumatoid arthritis (McCord 1974), acute respiratory distress syndrome (ARDS: Tate & Repine 1983), AIDS (Dröge et al. 1988), and more recently periodontal disease (Asman et al. 1984, 1986, Asman 1988, Henry et al. 1984, Hoffeld 1982, Kimura et al. 1993, Shapira et al. 1991, Whyte et al. 1989, Zafropoulos et al. 1991).

A free radical may be defined as "any species capable of independent existence that contains one or more unpaired elec-

trons" (Halliwell 1991). In recent years the term "reactive oxygen species" (or ROS) has been adopted to include molecules such as hydrogen peroxide ( $H_2O_2$ ), hypochlorous acid (HOCl) and singlet oxygen ( $^1O_2$ ), which whilst not radicals in nature, are capable of radical formation in the extra- and intracellular environments (Halliwell & Gutteridge 1990). Reactive oxygen species cause tissue damage by a variety of different mechanisms, which include the following:

- DNA damage.
- Lipid peroxidation (through activation of cyclooxygenases and lipoxygenases).
- Protein damage, including gingival hyaluronic acid and proteoglycans (Bartold et al. 1984).
- Oxidation of important enzymes, e.g. anti-proteases such as  $\alpha$ 1-antitrypsin (Varani et al. 1990).

• Stimulation of pro-inflammatory cytokine release by monocytes and macrophages, by depleting intracellular thiol compounds and activating nuclear factor  $\kappa$ B (NF- $\kappa$ B: Staal et al. 1990).

Whilst most ROS have extremely short half-lives ( $10^{-9}$ – $10^{-6}$  s, Pryor 1986), they can cause substantial tissue damage by initiating free radical chain reactions. It is therefore, not surprising that the body contains a number of protective antioxidant (AO) mechanisms, whose specific role is to remove harmful oxidants (or ROS) as soon as they form, or to repair damage caused by ROS in vivo. Antioxidants may be regarded as "those substances which when present at low concentrations, compared to those of an oxidisable substrate, will significantly delay or inhibit oxidation of that substrate" (Halliwell & Gutteridge 1989). Important AO's include the so-called "chain-breaking" antioxidants vitamin

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