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Oxidative Stress Pathway Driven by Inflammation in Gastric Mucosa

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1. Introduction

Oxidative stress is a state in which toxic reactive oxygen species (ROS) overcomes the endogenous antioxidant defence of the host (Bulger & Helton, 1998). This state results in an excess of free radicals, which can react with cellular lipids, proteins, and nucleic acids, leading to cellular injury and eventual organ dysfunction. Gastric inflammation is a highly complex biochemical protective response to cellular/tissue injury. A large amount of evidence suggests that *Helicobacter pylori* (H. pylori) infection and nonsteroidal anti-inflammatory drug (NSAID) ingestion are major causative factors in the pathogenesis of gastric mucosal oxidative injury in humans. In response to *H. pylori* infection or NSAID, neutrophils are recruited to the site of inflammation and generate ROS and nitrogen reactive species (RNS) (Yoshikawa & Naito, 2000; Naito & Yoshikawa, 2002). The sources of radicals are mucosal xanthine oxidase and NADPH oxidase found in the resident leukocytes of the lamina propria (Otamiri & Sjodahl, 1991). However, recent results suggest that NOX family of NADPH oxidases might also be expressed in gastric epithelial cells. ROS mediates inflammation by activating redox-sensitive transcription factors such as NF-kappaB and activator protein (AP)-1 which upregulate a number of proinflammatory genes, resulting in the production of proinflammatory cytokines, adhesion molecules, receptors, etc. The generation of ROS and cytokines not only that is associated but also amplifies each other (positive feedback regulation). Not only is increased ROS formation a trigger of inflammation but inflammation itself again triggers ROS production (Glorie et al., 2006).

2. Free radicals and oxidative stress

Free radicals are atoms or atomic groups that contain unpaired electrons. Since electrons have a very strong tendency to exist in a paired rather than an unpaired state, free radicals indiscriminately pick up electrons from other atoms, converting those other atoms into secondary free radicals. Thus a chain reaction is triggered that can cause substantial biological damage. Reactive oxygen species are oxygen-derived small molecules, including oxygen radicals [superoxide ($O_2^{\cdot -}$), hydroxyl ($^{\cdot}OH$), peroxyl ($RO_2^{\cdot}$), and alkoxyl ($RO^{\cdot}$)] and certain nonradicals that are either oxidizing agents and/or are easily converted into radicals, such as hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($^1O_2$), and hydrogen peroxide

(H_2O_2). RNS are nitrogen-containing oxidants, such as nitric oxide (Freitas et al. 2009,2010). The physiological generation of free radicals can occur as a byproduct of biological reactions in mitochondria, peroxisomes, cytochrome *P*-450. In a resting cell, superoxide anion is produced at 1–2% of total daily oxygen consumption during electron transfer and oxidative phosphorylation for ATP generation by mitochondria. Mitochondrial ROS are recognised as regulators of mitochondrial functions including electron transfer chain enzymes and mitochondrial membrane potential (Balaban et al., 2005, Finkel & Holbrook, 2005; Gottlieb, 2003). Overproduction of ROS, most frequently either by excessive stimulation of NADPH oxidase by cytokines, or by the mitochondrial electron transport chain and xanthine oxidase result in oxidative stress. Oxidative stress is a deleterious process that can be an important mediator of damage to cell structures and consequently various disease states and ageing (Jomova & Valko 2011; Valko, 2007).

During inflammation, phagocytic cells such as macrophages and neutrophils produce microbicidal oxidants whose formation is accompained by a transient episode of oxidative metabolism known as the respiratory burst. Reactive oxygen species, such as superoxide anion, hydrogen peroxide, the hydroxyl radical, and hypochlorous acid, together with microbicidal peptides and proteases, constitute their antimicrobial arsenal. The generation of microbicidal oxidants by neutrophils leads to the activation of a multiprotein enzyme complex known as the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is responsible for transferring electrons from NADPH to O_2, resulting in the formation of superoxide anion. This multicomponent enzyme system is composed of cytosolic proteins (p47phox, p67phox, p40phox, and rac1/2) and membrane proteins (p22phox and gp91phox, which form cytochrome b558) which assemble at membrane sites upon cell activation. NADPH oxidase activation is tightly regulated because of potential damage of surrounding tissues (Babior, 1999; Bedard & Krause, 2007; El Benna et al., 2005; Krause& Bedard, 2008). ROS generation is generally a cascade of reactions that starts with the production of superoxide. Superoxide rapidly dismutates to hydrogen peroxide either spontaneously, particularly at low pH or catalyzed by superoxide dismutase. The cascade of ROS generation include the reaction of superoxide with nitric oxide to form peroxynitrite, the peroxidase-catalyzed formation of hypochlorous acid from hydrogen peroxide, and the iron-catalyzed Fenton reaction leading to the generation of hydroxyl radical (Klebanoff, 1980). Free radicals may act as direct or indirect damaging agents through their reaction with other chemical or structural components in cells. ROS and RNS also recruit other inflammatory cells with secondary amplification of the damage. An enzymatic and non-enzymatic antioxidant defence systems, including catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) scavenge and regulate overall ROS levels to maintain physiological homeostasis. Lowering ROS levels below the homeostatic set point may interrupt the physiological role of oxidants in cellular proliferation and host defence. Under certain conditions, e.g., the presence of an elevated concentration of transition metal (Fe/Cu) ions, drug metabolism, or ischemia-reperfusion, ROS generation overwhelms cellular antioxidant defence resulting in oxidative stress. ROS may serve as cellular second messengers through the regulation of numerous signal transduction pathways at a concentration much below that required for formation of oxidative damage (Engelhardt et al., 2001). A rise in ROS levels may also constitute a stress signal that activates specific redox-sensitive signalling pathways. Once activated, these diverse signalling pathways may have either damaging or potentially protective functions (Finkel & Holbrook, 2000). Redox status has dual effects on upstream signaling system and downstream transcription factors.

Oxidants can stimulate many upstream kinases in signaling pathway cascades and yet inhibit transcription factors AP-1 and NF-kappaB activation (Kamata & Hirata, 1999). The signaling molecule, H_2O_2, mediates inflammation by activating NF kappaB and AP-1. Biological effects of NOX-derived O_2^- include: reaction with nitric oxide (NO) leading to NO degradation, peroxynitrite formation, protein tyrosine nitration, and the addition of glutathione (GSH) to thiols; reduction of iron centers within enzymes (e.g., aconitase) and alkalinization of intracellular organelles (Bedard & Krause, 2007). The current medical focus in this area has been directed toward the understanding of redox-driven physiological and pathophysiological processes in the cell.

3. Inflammation-induced oxidative stress in gastric mucosa

3.1 Ischemia- reperfusion injury-induced oxidative stress in gastric mucosa

Ischemia–reperfusion injury is important pathological process in gastric mucosal inflammation. Massive production of ROS during ischemia/reperfusion in turn lead to tissue injury. When production of ROS occurs in an uncontrolled manner, the result is excessive cellular/tissue damage that results with chronic inflammation and destruction of normal tissue (Yoshikawa & Naito, 2000; Sasaki & Joh, 2007). Neutrophils are the principal effector cells of reperfusion injury. Under the conditions of ischemia/ reperfusion, xanthine dehydrogenase is converted into xanthine oxidase which uses oxygen as a substrate. During ischemia, utilisation leads to a depletion of ATP and accumulation of the purine catabolites hypoxanthine and xanthine, which are metabolized by xanthine oxidase to produce enormous amounts of superoxide radical and hydrogen peroxide upon subsequent reperfusion and influx of oxygen (Granger et al., 2001).

In the extracellular space adenosine and ATP act as important endogenous signaling molecules in immunity and inflammation through activation of purinergic receptors (Swenen et al., 2005). Swennen et al. examined the ex vivo immunomodulatory effects of ATP in whole blood from healthy subjects. These data indicate that ATP is an anti-inflammatory agent with simultaneous TNF-alfa suppressing and IL-10 augmenting activity.In addition, ATP has been shown to contribute to the initiation of oxidative burst. It appears to prime neutrophils for functional responses to various inflammatory mediators, as indicated by increased production of ROS (Fredholm, 1997; Zhang et al., 1996). Endoscopic studies using reflectance spectrophotometry and laser Doppler flowmetry have reported a decrease in mucosal blood flow resulting in impairment of gastric mucosal energy metabolism. Adenine nucleotides in biopsy samples from human gastric mucosa were measured using high-performance liquid chromatography (HPLC).

Energy charge (EC) was assessed from ATP, adenosine diphosphate (ADP) and adenosine monophosphate (AMP) and calculated as EC=ATP + 1/2 ADP)/ATP + ADP + AMP. Energy charge of antrum was lower compared to corpus in the gastric mucosa. In elderly, the impaired energy metabolism in human gastric mucosa may weaken their defensive mechanism (Kawano et al., 1991). In vitro studies suggest that extracellular nucleotides and nucleosides may be important regulators of inflammatory and immune responses (Di Virgillio et al., 2001). Acute gastric erosions following hemorrhagic shock (stress ulceration) have been attributed to gastric hyperacidity, altered gastric secretion of mucus and an abnormal permeability of the gastric mucosa to H^+. An energy deficit severe enough to cause cellular necrosis is the event linking shock-induced gastric mucosal ischemia and stress ulceration (Menguy & Master 1974a, 1974b, 1974c, 1974d). This studies support the

value of ATP as a highly potent natural compound, which able to modulate inflammation and oxidative stress.

The conditions of chronic inflammation predispose susceptible cells to neoplastic transformation. ROS appear to be the key regulatory factors in molecular pathways linked to tumour development and tumour dissemination (Valko, 2007).

The longer the inflammation persists, the higher the risk of cancer gets. Inflammatory processes may induce DNA mutations in cells via oxidative/nitrosative stress. Inflammatory cells and cancer cells themselves produce free radicals and soluble mediators such as metabolites of arachidonic acid, cytokines and chemokines, which act by further producing reactive species. These, in turn, strongly recruit inflammatory cells in a vicious cycle. Reactive intermediates of oxygen and nitrogen may directly oxidize DNA, or may interfere with mechanisms of DNA repair. The main substances that link inflammation with cancer via oxidative/nitrosative stress are prostaglandins and cytokines. The effectors are represented by an imbalance between pro-oxidant and antioxidant enzyme activities (lipoxygenase, cyclooxygenase and phospholipid hydroperoxide glutathione-peroxidase), hydroperoxides and lipoperoxides, aldehydes and peroxinitrite (Federico et al., 2007).

3.2 *Helicobacter pylori*-induced oxidative stress

Helicobacter pylori, a pathogenic bacterium, is highly adapted to its ecologic niche, the human gastric mucosa. The pathogenesis of *H. pylori* relies on its persistence in surviving a harsh environment, including acidity, peristalsis, and oxidative burst by phagocyte cells (McGee & Mobley, 1999). *H. pylori* infection causes chronic inflammation, accumulation of ROS and oxidative DNA damage in the gastric mucosa.

During the process of colonizing the host, *H. pylori* induces a strong inflammatory response, generating large amounts of ROS. To evade oxidative killing *H. pylori* prevents NADPH oxidase assembly at the phagosome, with release of NADP+ and large amounts of superoxide anions into the extracellular milieu (Allen, 2007a; Allen, 2007b). *H. pylori* injects bacterial proteins into the cytosol of the gastric host cell *via* the type IV injection system and regulates the intracellular signal transduction. This mechanism provides a approach to resolving how *H. pylori* survives in the acidic environment of the human stomach. (Suzuki, 2006a, 2006b).

A number of studies have shown that *H. pylori* infection is associated with generation of free radicals, which leads to oxidative stress in the gastric mucosa (Fukuhara et al., 2008; Davies et al. 1994a, 1994b; McGee & Mobley 1999; Pignatelli et al., 2001; Li et al., 2001; Baik et al., 1996). Exposure of gastric epithelial cells to *H. pylori* resulted in an inflammatory reaction with production of ROS and nitric oxide (Nardone et al., 2004).The effects of bacterial eradication on mucosal oxidative stress were investigated by measuring the changes of the expression of inducible nitric oxide synthase (iNOS) and levels of nitrotyrosine and 8-hydroxy-2|[prime]|-deoxyguanosine in antral biopsies from patients with chronic atrophic gastritis and peptic ulcer disease before and after bacterial eradication. *Helicobacter pylori* eradication attenuates oxidative stress in human gastric mucosa (Pignatelli et al., 2001). The adding of prescribed doses of vitamins E and C to antimicrobial therapy is effective in eradicating *H. pylori* infection (Sezikli et al., 2009). Recent studies demonstrated that increased levels of ROS are generated in *H. pylori*- infected gastric epithelial cells and that this may be one mechanism leading to apoptosis associated with infection **(**Ding et al., 2007). Host intracellular iron has been noticed as an important cofactor in induction of NADPH-dependent oxidative burst. The changed equilibrium of intracellular iron could influence the

course of infection to the enhancement of the pathogen with regard to oxidative stress (Dovhanj et al., 2009).

The expression of eight proteins (78 kDa glucose-regulated protein precursor, endoplasmin precursor, aldehyde dehydrogenase 2 and L-lactate dehydrogenase B chain, intracellular chloride channel protein 1, glutathione S-transferase, heat-shock protein 60 and cytokeratin 8) were altered in the *H. pylori*-infected tissues compared with the non-infected tissues. These proteins are related to cell proliferation, carcinogenesis, cytoskeletal function and cellular defence mechanism. *H. pylori*-induced alterations of protein expression of these proteins indicate the involvement of oxidative stress in the pathogenesis of *H. pylori*-induced gastric diseases, including inflammation, ulceration and carcinogenesis (Baek et al., 2004).

3.3 Role of glutathione and Mn-SOD in oxidative stress -induced gastric mucosal injury

The NADPH oxidase complex causes a strong stimulation of the pentose phosphate pathway (PPP), which primarily control the most important antioxidant of gastric mucosa, glutathione (Beil et al. 2000; Matthews & Butler, 2005).

Glutathione is a co-substrate of many enzymes involved in cellular detoxification and protection mechanisms (Townsend & Tew 2003). Maintaining optimal reduced glutathione/oxidized glutathione (GSH/GSSG) ratio in the cell is critical to survival and tight regulation of the system is imperative. A deficiency of GSH puts the cell at risk for oxidative damage (Townsend et al., 2003). *H. pylori* directly decrease cellular glutathione. Concerning GSH, their recycling is dependent on the maintenance of an pool of NADPH mainly via the pentose phosphate pathway, in which the reaction catalyzed by the glucose-6-phosphate dehidrogenase (G6-PDH) is the rate-limiting step. Mutations in *ZWF1*, the gene which encodes G6-PDH, make cells hypersensitive to oxidants such as H_2O_2 (Juhnke et al., 1996). During normal detoxification, H_2O_2 is converted to H_2O by reduced glutathione peroxidase and the oxidized glutathione is converted back to the reduced form by glutathione reductase and NADPH.

Glutathione (gamma-L-glutamyl-L-cysteinylglycine), the main non-protein thiol found in cells, is synthesized exclusively in the cytosol in two steps that require ATP. The first step is the unusual coupling of the gamma-carboxylic acid of glutamic acid to cysteine by the enzyme gamma-glutamylcysteine synthetase, followed by the formation of GSH by GSH synthetase, which uses ATP and gamma-glutamylcysteine and glycine as substrates. The formation of gamma-glutamylcysteine is the rate-limiting reaction in GSH synthesis and is a feedback inhibited by GSH itself, a mechanism responsible for the regulation of cellular GSH concentration.

Glutathione S-transferase plays a key role in the detoxification of carcinogenes, therapeutic drugs, and products of oxidative stress. This enzyme utilizes glutathione in reactions contributing to the transformation of such substances.

Studied association between glutathione S-transferases polymorphisms and immunoglobin G titer levels in serum against *Helicobacter pylori* in healthy subjects seropositive for *H. pylori* suggests that glutathione S-transferases activity is possibly involved in the protection against mucosal atrophy caused by *H. pylori* (Tatemichi et al., 2009). Another data showed that GSH plays a major role in cytoprotection against ulceration (Demir et al., 2003). This study has shown that gastric mucosal malondialdehide (MDA) levels were significantly higher, and gastric mucosal concentrations of GSH were significantly lower in peptic ulcer and gastritis patients compared to controls. These results suggest that the depletion of

gastric mucosal glutathione in peptic ulcers and gastritis is caused by accumulation of free radicals. The findings of the study also confirm that ROS play important pathological role in gastric mucosa. Therefore, effective treatment and prevention of gastritis and peptic ulcers should be based on using the antioxidants in order to enhance gastric mucosal defence. Antioxidant enzymes, superoxide dismutase catalase, glutathione peroxidase, or peroxiredoxins are vital to the regulation of oxidative stress within cells. Significant changes in the activity and expression of several isoforms of superoxide dismutase were observed in the human gastric disease.

In eukaryotic cells, three isoforms of superoxide dismutase are present: extracellular copper/zinc-containing SOD (EC-SOD), mitochondrial manganese containing SOD (Mn-SOD), and cytoplasmic/nuclear copper/zinc-containing SOD (Cu,Zn-SOD), although the latter also localizes to the mitochondrial intermembrane space (Okado-Matsumoto & Fridovich, 2001). While the SOD isoenzymes catalyze the identical dismutation reaction involving the conversion of superoxide anion to oxygen and hydrogen peroxide , the function of each SOD isoform in cellular physiology appears to be very different, and often one SOD cannot compensate for another. Manganese superoxide dismutase induced by oxidative stress and by several physiological stimuli including inflammatory cytokines, bacterial proteins and growth factors. Gotz *et al*. first reported an increase of Mn- SOD in *H. pylori* -positive gastric mucosa. The study showed a significant correlation between the level of Mn-SOD protein with the degree of inflammation in the gastric mucosa (Noguchi *et al*., 2002; Smoot et al., 2000). Recently, we have reviewed the important role of Mn-SOD in inflammation (Dovhanj et al., 2010). Manganese superoxide dismutase expression has been evaluated in gastric cancer, but little is known about the expression changes that occur in Mn-SOD in normal gastic mucosa from non-cancer patients with chronic gastritis. The evaluation of Mn-SOD activity during inflammation of gastric mucosa could clear out whether its assessment may be important to prevent the accumulation of gastric epithelial cell oxidative damage.

Given the risk of Mn-SOD overexpression and the role of Mn-SOD in the response to oxidative stress we hypothesized that patients with chronic gastritis would have increased mucosal Mn- SOD expression associated with chronic inflammation in the gastric mucosa. The inverse correlation between Mn-SOD activity and cell growth is a paradoxical phenomenon because Mn-SOD functions only as an antioxidant enzyme to protect a cell from oxidative stress caused by $O_2^{\cdot-}$ (Oberley, 2001). Proposed hypotheses regarding mechanisms by which Mn-SOD exerts growth inhibition often emphasize increased H_2O_2 production secondary to elevated Mn-SOD activity resulting in oxidative environments first in mitochondria and subsequently in the cytoplasm (Li et al., 2001; Li & Oberley, 1998; Rodriguez et al., 2000).

Reactive oxygen species and glutathione levels were measured in various phases of the cell cycle in both parental NIH/3T3 cells and NIH/3T3 cells overexpressing Mn-SOD, to determine whether their levels could have a possible regulatory role in cell cycle progression. This results suggest that oxidative stress exists in M phase of the cell cycle with total glutathione levels increased to decrease oxidative stress while analysis of Mn-SOD-overexpressing cell clones showed correlation of decreased cell growth with an ROS increase in S phase of the cell cycle and decrease of glutathione in mitosis. The data strongly suggest that specific levels of cell redox state are necessary for cells to successfully progress through the various phases of the cell cycle (Li & Oberley, 1998).

However, overexpression of Mn-SOD exceeding physiological conditions can lead to accumulation of ROS and oxidative stress, which may contribute to tumor metastasis and angiogenesis. It is known that intracellular content of Mn-SOD is altered in gastric neoplasms compared with normal tissue (Janssen et al., 2000; Hermann et al., 2005; Kruidenier et al., 2003, Hwang et al., 2005). Mn-SOD overexpression inhibits cell growth in both nonmalignant and malignant cells. The studies on Mn-SOD expression in cancer cells have been conducted on human tumours by comparing the specific cancer cell type with a relevant control cell type (colorectal cancer/ adjacent normal mucosa, oesophageal and gastric cancer /normal mucosa). According to these studies, Mn-SOD expression is variable but often high in human tumours compared to their normal counterparts. Understanding of the regulation of antiproliferative pathways by Mn-SOD and its control of tumor invasion might aid in the design of novel therapies targeting the respective molecular pathways (Valko, 2007).

4. Oxidative damage to DNA, lipids and proteins

The inflammation of gastric mucosa activates various oxidant-producing enzymes such as NADPH oxidase and inducible nitric oxide synthase. Reactive oxygen metabolites and nitrogen metabolites generated by these enzymes react with each other to generate new or more potent reactive species. The specific types of cellular damage resulting from reactive oxygen metabolites include lipid peroxidation, protein oxidation, and oxidative DNA damage. At high concentrations, ROS can be important mediators of damage to cell structures. Consequences of this stress include modification to cellular proteins, lipids and DNA (Valko et al., 2006). The hydroxyl radical is known to react with all components of the DNA molecule, damaging both the purine and pyrimidine bases and also the deoxyribose backbone (Halliwell & Gutteridge, 1999). The most extensively studied DNA lesion is the formation of 8-nitroguanine while carbonyl derivatives of proteins are the most widely studied oxidative stress-induced protein modifications (Valko et al., 2007). Carbonyl formation can occur through a variety of mechanisms including direct oxidation of certain amino-acid side chains and oxidation-induced peptide cleavage. Although all organs and all proteins can potentially be modified by oxidative stress, certain tissues and specific protein targets may be especially sensitive (Stadtman, 1992; Yan at al., 1997). The side chains of all amino acid residues of proteins, in particular cysteine and methionine residues of proteins are susceptible to oxidation by ROS/RNS (Stadtman, 2004). Oxidation of cysteine residues may lead to the reversible formation of mixed disulphides between protein thiol groups (–SH) and low molecular weight thiols, GSH (*S*-glutathiolation). The concentration of carbonyl groups, generated by many different mechanisms is a good measure of ROS-mediated protein oxidation. A number of highly sensitive methods have been developed for the assay of protein carbonyl groups (Dalle-Donne, 2005).

Nitric oxide contributes to oxidative lesions and alterations of gastric mucosa structure. Urinary 8-nitroguanine, a product of nitrative nucleic acid damage caused by reactive nitrogen species such as peroxynitrite and nitrogen dioxide. Immunoreactivity of the 8-nitroguanine has been found in the cytosol as well as in the nucleus of inflammatory cells and epithelial cells in inflamed tissues, but not in normal tissues. 8-nitroguanine in DNA is potentially mutagenic, yielding G:C to T:A transversion, possibly through its rapid depurination to form an apurinic site and/or miscoding with adenine. 8-nitroguanine in RNA may interfere with RNA functions and metabolism. Nitrated guanine nucleosides and

nucleotides in the nucleotide pool may contribute to oxidative stress via production of superoxide mediated by various reductases and may disturb or modulate directly various important enzymes such as GTP-binding proteins and cGMP-dependent enzymes (Ohshima, et al. 2006).

Determination of NO metabolites concentrations in gastric juice of *Helicobacter pylori* positive patients has shown that the increase of NO metabolites is correlated with inflammatory lesions in gastric mucosa (Walecka-Kapica, E., 2008). *Helicobacter pylori* infection is associated with oxidatively damaged DNA in human leukocytes and decreased level of urinary 8-oxo-7,8-dihydroguanine. The levels of 8-oxo-7,8-dihydroguanine in DNA isolated from leukocytes of *H.pylori* infected patients and in the group with gastritis without *H.pylori* infection were significantly higher than in DNA isolated from the control group while level of urinary 8-oxo-7,8-dihydroguanine of children infected with *H.pylori* was significantly lower compared to group with gastritis without *H.pylori* infection. This increase of 8-oxo-7,8-dihydro-2'-deoxyguanosine level in leukocytes was interpreted as a response to inflammation itself, not just *H.pylori* infection. However, observed decrease in the level of modified base in urine seems to be specific for *H.pylori* infection and possibly linked with nitric oxide mediated inhibition of a key base excision repair enzyme (human 8-oxo-7, 8-dihydroguanine glycosylase) responsible for the repair of 8-oxo-7,8-dihydroguanine (Siomek, 2006).

Amelioration of oxidative stress with ensuing inflammation contributes to chemoprevention of *H. pylori*-associated gastric carcinogenesis (Park 2004). Gastric mucosa of patients infected by CagA-positive strains is characterized by a higher generation of ROS and by greater neutrophil counts than that observed in CagA-negative subjects (Danese, 2001). In addition, the oxygen-free radicals-mediated damage due to *H. pylori* cytotoxic strains, CagA+ strains, could be a driving force that leads from chronic gastritis to gastric carcinoma (Papa, 2002). A double immunofluorescence labeling study demonstrated that the level of 8-nitroguanine and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) apparent in gastric gland epithelium was significantly higher in gastritis patients with *H. pylori* infection than in those without infection. This results suggest that 8-nitroguanine could be a promising biomarker of inflammation (Ma, 2004).

Kawanishi et al. examined the formation of 8-nitroguanine, a nitrative DNA lesion, in humans and animals under inflammatory conditions. An immunofluorescence labeling study demonstrated that 8-nitroguanine was strongly formed in gastric gland epithelial cells in gastritis patients with *H. pylori* infection, in hepatocytes in patients with hepatitis C, and in oral epithelium of patients with oral lichen planus. 8-nitroguanine was also formed in colonic epithelial cells of model mice of inflammatory bowel diseases and patients with ulcerative colitis. Interestingly, 8-nitroguanine was formed at the sites of carcinogenesis regardless of etiology. Therefore, 8-nitroguanine could be used to evaluate the risk of inflammation-related carcinogenesis.

Oxidative damage of the gastric mucosa in *H. pylori* positive chronic atrophic and nonatrophic gastritis, was evaluated by nitrotyrosine immunohistochemistry in the mucosa before and after eradication. Total nitrotyrosine levels appeared significantly higher in *H. pylori* positive than in negative patients. Oxidative damage of the gastric mucosa increases from *H. pylori* -chronic gastritis to *H. pylori* - chronic atrophic gastrits, involving the foveolae and intestinal metaplasia. *H. pylori* eradication induces a complete healing of foveolae but not of intestinal metaplasia, reducing the overall oxidative damage in the mucosa (Iacopini, F. et al. 2003). *Helicobacter pylori* eradication has differential effects on oxidative DNA

damage at the gastroesophageal junction and at the gastric antrum. The levels of DNA adducts in the antral mucosa are not modified by *H. pylori* eradication; conversely, *H. pylori* eradication significantly increases the oxidative adducts at the gastroesophageal junction (Farinti, 2004).

Enhanced understanding of the mechanisms of gastroduodenal defense and injury provides new insight into potential therapeutic targets, contributing towards the development of better tolerated and more effective therapies (deFoneska 2010). Albayrak et al, 2010 suggested that urinary 8-OHdG levels could be investigated in every patient with chronic gastritis, since it is a simple and completely noninvasive procedure. In patients with high levels of urinary 8-OHdG, endoscopic procedures or even pathological investigation may then be carried out, with the consideration that there is a high risk of intestinal metaplasia.

4.1 Monitoring of oxidative damage of gastric mucosa

The determination of oxidative stress in inflammation of gastric mucosa may be important for a better understanding of its pathophysiology. ROS and RNS react with each other to generate new or more potent reactive species. Specific types of cellular damage resulting from reactive oxygen metabolites include lipid peroxidation, protein oxidation, and oxidative DNA damage. There are direct and indirect markers for monitoring of oxidative damage of gastric mucosa. Measurement of oxidation markers (direct) is helpful to assess oxidant activity and to monitor the effectiveness of the antioxidant system in normal cell affected by inflammation. The techniques range for detecting free radicals and reactive oxygen species or their byproducts include advanced methodologies using high-performance liquid chromatography, mass spectrometry, and electron paramagnetic resonance. The HPLC techniques are applied to the electrochemical measurement of protein oxidation products, particularly nitrotyrosine and dityrosine, and to the electrochemical detection of DNA oxidation products (Sawa, 2006). There are also mass spectrometry methods for measuring lipid oxidation products. Determination of biological markers of in vivo oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, and well-known lipid peroxidation markers, malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) are important for oxidative damage of gastric mucosa . HNE and MDA produce DNA adducts such as exocyclic etheno- and propano-DNA adducts, which are strong promutagenic DNA lesions causing point mutations.

The enzymatic and nonenzymatic antioxidants have been proposed as indirect markers. Among them, ascorbic acid, a-tocopherol, glutathione, enzymatic redox system of glutathione, glutathione-S-transferase and superoxide dismutase are related to gastric mucosal damage. Urinary hydrogen peroxide was postulated to be a biomarker of oxidative stress. (Baneerje, 2003). Recently, Lianzhen Yu et al. studied the low-molecular-weight 15 metabolites (including antioxidants) in blood plasma to characterize different stages from chronic superficial gastritis to chronic atrophic gastritis, intestinal metaplasia, gastric dysplasia and finally gastric cancer. They applied gas chromatography time-of-flight mass spectrometry to determine metabolites levels in plasma. The discriminatory metabolites characterizing progressive stages from chronic superficial gastritis to gastric cancer might be the potential markers to indicate the risk of gastric cancer. After a critical review of the literature data, we conclude that the balance between antioxidants and by-products of oxidative stress in the organism might be the best approach for the evaluation of oxidative stress in patients with gastric mucosal inflammation.

5. Conclusion

The severity of active inflammation of infected mucosa is directly correlated to the presence of high concentrations of free radicals. Increased oxidative stress in normal mucosa that had undergone changes in intensity of inflammatory infiltrates in the lamina propria are due to presence of inflammatory cells within the gastric mucosa. The inflammation has a key promoting role in oxidative stress. During the inflammation, inflammatory cells migrate to the injured site followed by a respiratory burst generating superoxide anion and other ROS. Oxidants, as mediators of cell damage, should be eliminated in normal cells. Antioxidative enzyme, Mn-SOD, is critically important in the maintenance of mitochondrial function in a cell. Thus, the mitochondrial Mn-SOD represents a major cellular defense against oxidative stress. A number of studies have suggested that altered cell redox state prove oxidative stress in gastric mucosa and further strengthen the idea of antioxidative defence up-regulation as protection of normal cells against inflammatory cells-derived ROS. The precise mechanisms of association between inflammation of gastric mucosa and mucosal oxidative damage need to be evaluated. Previous findings support the general idea that the evaluation of oxidative stress could be a useful factor for estimating the importance of the inflammation of gastric mucosa.

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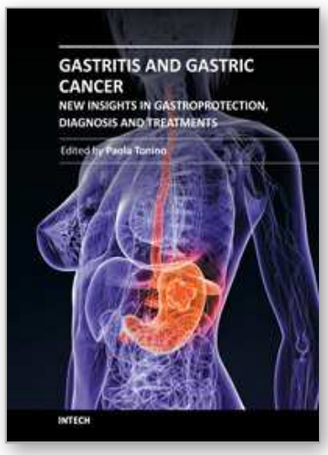

Gastritis and Gastric Cancer - New Insights in Gastroprotection, Diagnosis and Treatments

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This book is a comprehensive overview of invited contributions on Helicobacter pylori infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in H. pylori related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in H. pylori infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with H. pylori infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and H. pylori lipopolysaccharide, as well as the roles of several bacterial genes (cagA, cagT, vacA and dupA) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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