Review article

OXIDATIVE STRESS RELATED APOPTOSIS IN SMOKERS AND CHRONIC LUNG DISEASES

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Abstract

Cigarette smoke contains various carcinogens, reactive oxygen species (ROS) and reactive nitrogen species (RNS). It has been found that cigarette smoking causes several chronic lung diseases including chronic obstructive pulmonary diseases (COPD). There are multiple markers used for oxidative damage/stress in smokers such as urinary 8-hydroxydeoxyguanosine (8-OHdG), serum hydrogen peroxide (H2O2), interleukin-8 (IL-8) and H2O2 in breath condensate. The levels of nitrated proteins (fibronectin, transferrin, and plasminogen) are higher in smokers than in non-smokers. The 4-HNE (4-hydroxynonenal) is higher in alveolar epithelial cells, neutrophils and endothelial cells in smokers. The proinflammatory genes, e.g. TNF-α (tumor necrosis factor-α), stress response genes and antioxidant enzymes such as superoxide dismutase (SOD) and thioredoxin are induced in bronchial epithelial cells and alveolar macrophages. Oxidative stress upregulates antioxidant genes, e.g. γ-glutamylcysteine synthetase (an enzyme that synthesizes glutathione). ROS have roles in nuclear transcription factor activation and phosphorylation such as activator protein-1 (AP-1) and the mitogen-activated protein kinase (MAPK) family in inducing inflammatory and antioxidant genes. Apoptosis occurs more frequently in the spermatozoa and placental syncytiotrophoblasts of smokers than in non-smokers. Smoking also perturbs the normal pattern of fibrin deposition in placental intervillous spaces. Furthermore, carotenoids modulate intracellular redox state, and are involved in the regulation of cell cycle progression and apoptosis of pulmonary cells in smokers. Chiang Mai Med Bull 2006;45(4):173-184.

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Reactive oxygen species (ROS) such as superoxide anion (O2−) and the hydroxyl radical (OH) are unstable molecules with unpaired electrons, capable of initiating oxidation.

Biological systems are exposed to oxidants that are generated endogenously by metabolic reactions; e.g. from the mitochondrial electron transport chain during oxidative phosphoryla-
tion, while activating phagocytes, or exogenously, e.g. by air pollutants or cigarette smoke.

The lung exists in a high-oxygen environment and, together with its large surface area and blood supply, is susceptible to injury mediated by ROS. Production of ROS has been directly linked to oxidation of proteins, DNA, and lipids, which cause direct lung damage or induce various cellular responses through the generation of secondary metabolic reactive species.

ROS may result in remodeling of the extracellular matrix, causing apoptosis and enhancing cell proliferation. Alveolar repair responses and immune modulation in the lung may also be influenced by ROS.\(^{1}\) In addition, high levels of ROS have been implicated in initiating inflammatory responses through activation of transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), and thus signal transduction and gene expression of inflammatory mediators.\(^{2,3}\)

It is proposed that ROS produced by phagocytes, which have been recruited to sites of inflammation, are a major cause of cell and tissue damage associated with many chronic inflammatory lung diseases, including chronic obstructive pulmonary diseases (COPD) and asthma.\(^{4}\)

**Cells and ROS**

The activation of macrophages, neutrophils and eosinophils generates O$_2^-$, which is rapidly converted to H$_2$O$_2$ under the influence of superoxide dismutases (SOD), and OH is formed nonenzymatically in the presence of Fe$^{2+}$ as a secondary reaction. ROS and RNS can also be generated intracellularly from several sources such as mitochondrial respiration, the NADPH oxidase system, and xanthine/xanthine oxidase. In addition to NADPH oxidase, phagocytes employ other enzymes to produce ROS, which involve the activity of heme peroxidases myeloperoxidases, MPO or eosinophil peroxidases (EPO).\(^{5,6}\)

EPO results in the formation of potent oxidant hypochlorous acid (HOCl) and hypobromous acid (HOBr) from H$_2$O$_2$ in the presence of chloride (Cl$^{-}$) and bromide (Br$^{-}$) ions, respectively. Eosinophils substantially produce oxidants because these cells possess several times greater capacity than neutrophils to generate O$_2^-$ and H$_2$O$_2$, and the content of EPO in eosinophils is 3-10 times higher than the amount of MPO present in neutrophils. HOBr reacts rapidly with a variety of nucleophilic targets such as thiols, thiol ethers, amines, unsaturated groups and aromatic compounds.\(^{5}\)

**Cigarette smoke and ROS**

Cigarette smoking is a serious health problem in society. It is known that cigarette smoke is a cell mutagen and carcinogen. Cigarette smoking is associated with increased nitric oxide (NO) production and increased oxidative stress in the airways, with an increased risk of degenerative diseases.

Aqueous extracts of cigarette smoke were irradiated with UV, and hydroxyl radical generation was evaluated by electron spin resonance (ESR). The spectra obtained revealed spin adducts of the hydroxyl radical (OH) which increased with the aqueous extract volume of cigarette smoke, cigarette smoke collection flow and UV irradiation time. Hydroxyl radical generation persisted for many hours, showing no change over time. In specimens of urine from volunteers, 8-hydroxydeoxyguanosine (8-OHdG) levels and the 8-OHdG-production per hour were found to be higher in smokers than in non-smokers.\(^{7}\)
Cigarette smoking or inhalation of airborne pollutants that may be either oxidant gases, e.g. ozone, nitrogen dioxide ($\text{NO}_2$) and sulfur dioxide ($\text{SO}_2$), or particulate matter in air pollution, results in direct lung damage as well as the activation of inflammation in the lungs. Cigarette smoke is a complex mixture of over 4,700 chemical compounds, including high concentrations of oxidants ($10^{14}$ molecules per puff).\(^8\) Short-lived oxidants such as $\text{O}_2^-$ and nitric oxide (NO) are predominantly found in the gas phase.

The massive health problem associated with cigarette smoking is exacerbated by the addictive properties of tobacco smoke and the limited success of the current approach to cessation of smoking. Yet little is known about the neuropharmacological actions of cigarette smoke that contribute to smoking behavior, or why smoking is so prevalent in psychiatric disorders, and associated with a decreased risk of Parkinson’s disease. It was reported that the brains of living smokers show a 40% decrease in the level of monoamine oxidase B (MAO B; EC1.4.3.4) in relation to non-smokers or former smokers. MAO B is involved in the breakdown of dopamine, a neurotransmitter implicated with enhanced dopamine activity, as well as decreased production of $\text{H}_2\text{O}_2$.\(^9\)

Cigarette smoking is associated with increased nitric oxide (NO) production and increases in $\text{H}_2\text{O}_2$ concentration (or increased oxidative stress) in the airways. $\text{H}_2\text{O}_2$ is increased in exhaled breath condensate of asthmatic subjects and may be used as a non-invasive marker of oxidative stress.\(^10\)

Cigarette smoking is a major risk factor in atherosclerosis and a useful model from which to study chronic inflammation. Smokers incur a sustained free radical load that may increase the antioxidant requirement. It was found that plasma concentrations of lipid peroxides, thiobarbituric acid reactive substances, and conjugated dienes were also elevated significantly in smokers compared with non-smokers.\(^11\) Smokers also have lower serum HDL-cholesterol compared to non-smokers.\(^12\) Furthermore, it has been reported that the mean serum $\text{H}_2\text{O}_2$ level of non-smokes is lower than that of smokers.\(^13\)

Moreover, cigarette smoking has been associated with accelerated follicular depletion and derangement of reproductive functions, e.g. lower fertilization rate when compared to non-smokers. It was found that follicular fluid contained a lower level of $\beta$-carotene in response to oxidative stress imposed by cigarette smoke.\(^14\)

**Oxidative stress in smokers and patients with COPD**

More than 90% of patients with COPD are smokers, but not all smokers develop COPD. An increased oxidant burden in smokers derives from many kinds of ROS released from macrophages and neutrophils. Both neutrophils and macrophages are known to migrate into the lungs of cigarette smokers in increased numbers when compared with non-smokers.\(^4\) Cigarette smoking is associated with an increase in MPO in neutrophils, which correlates with the degree of pulmonary dysfunction.\(^15\)

Hydrogen peroxide, measured in exhaled breath, is a direct measurement of oxidant burden in airspace. Smokers and patients with COPD have higher levels of exhaled $\text{H}_2\text{O}_2$ than non-smokers, and the levels are even higher during exacerbation of COPD. The generation of ROS in epithelial lining fluid may be enhanced further by the presence of an increased amount of free iron in the airspace.
in smokers. This is relevant to COPD, since compared to non-smokers the intracellular iron content of alveolar macrophages is increased in cigarette smokers, who increase it further if they develop chronic bronchitis.\

Other studies have shown that circulating neutrophils from patients with COPD show upregulation of their surface adhesion molecules, which may also be an oxidant-mediated effect. There have been reports of increased levels of NO in the exhaled breath of patients with COPD, but they are not as high as the levels reported in asthmatics. Smoking increases NO levels in exhaled air, and the reaction of NO with $O_2^-$ limits the usefulness of the marker in COPD, except perhaps to differentiate from asthma.\

Oxidative stress caused by airway inflammation is increased in COPD and may account for the progressive deterioration of structure and function of the respiratory tract observed in this disease. The level of $H_2O_2$ concentration in exhaled air condensate (EAC) is a valuable tool for assessing and monitoring oxidative stress.\

It was found that in COPD patients, $H_2O_2$ in exhaled air, IL-8 and the soluble cell adhesion molecule sICAM, and sE-selectin in serum were raised in comparison with a control group. During treatment with prednisolone, $H_2O_2$ concentrations in breath condensate declined significantly as well as IL-8 and sICAM.\

The correlation between susceptibility to peroxidation, and the polyunsaturated fatty acid (PUFA) content of red blood cells before supplementation, suggest an inadequate intake of vitamin E in relation to PUFA intake. The requirement for vitamin E appears to be greater in smokers than in non-smokers. Moreover, urinary 8-hydroxydeoxyguanosine (8-OHdG) was used as a biomarker of oxidative DNA damage, whereas plasma nitric oxide (NO) was measured as an indicator of oxidative stress related to traffic exhaust exposure in smokers and non-smokers. However, there is also a report on determinations of oxidative stress, with 2-thiobarbituric acid for malondialdehyde and 5,5'-DTNB (dithiobisnitrobenzoic acid) for thiol groups.\

NO and $O_2^-$ react immediately to form a highly reactive peroxynitrite (ONOO-) molecule. The radicals in the tar phase of cigarette smoke are organic, such as long-lived semiquinone radicals, which can react with $O_2^-$ to form OH and $H_2O_2$. The tar phase is also a metal chelator and can bind iron to produce tar semiquinone and tar-Fe$^{2+}$, which can generate $H_2O_2$ continuously. Aqueous extracts of cigarette tar contain the quinone radical, (Q-) which can reduce oxygen to form $O_2^-$ and then dismutate to form $H_2O_2$. Further- more, since both cigarette tar and lung epithelial lining fluid contain metal ion, such as iron, Fenton reaction will result in the production of OH, which is a highly reactive and potent ROS. It has been suggested that oxidants from pulmonary inflammatory cells may contribute to the development of emphysema by direct tissue toxicity and inhibition of $\alpha_1$-antitrypsin, thus diminishing protection of the lung from proteolytic damage. It was demonstrated that more $H_2O_2$ was released from alveolar macrophages (AM) of smokers than in non-smokers. This finding is consistent with the hypothesis that $H_2O_2$ of AM origin contributes to the development of emphysema in smokers. There is evidence of increased oxidative stress in the airways of patients with COPD that is increased further by severe and very severe exacerbation of the disease. This is associ-
Oxidative stress related apoptosis in smokers

Cigarette smoking increases the formation of RNS and results in nitration and oxidation of plasma proteins. The levels of nitrated proteins (fibrinogen, transferrin, plasminogen, and ceruloplasmin) are higher in smokers than in non-smokers. Nitric oxide and ONOO- mediated formation of 3-nitrotyrosine in plasma, and free catalytic iron (Fe^{2+}) levels in epithelial lining fluid are elevated in chronic smokers.

The 4-HNE (4-hydroxynonenal) is a highly reactive and specifically diffusible end-product of lipid peroxidation. The 4-HNE-modified protein levels present in alveolar epithelial cells, endothelial cells, and neutrophils are increased in smokers with airway obstruction when compared to subjects without airway obstruction. This demonstrates not only the presence of 4-HNE, but also that 4-HNE has modified proteins in the lung cells of patients with COPD to a greater degree. Isoprostanes are products of nonenzymatic lipid peroxidation and have therefore been used as markers of oxidative stress. The isoprostanes are ROS catalyzed isomers of arachidonic acid and stable lipid peroxidation products, which circulate in plasma and are excreted in urine. The levels of lipid peroxides such as 8-isoprostane and hydrocarbons, like ethane and pentane, are increased in the exhaled air condensate of smokers and patients with COPD. Moreover, it was reported that malondialde-hyde (MDA), hyaluronan (HA), and vitamin E in tracheal aspirate fluid (TAF) may be used as biochemical markers for the prognosis of chronic lung diseases.

**Proinflammatory gene expression**

Inflammatory mediators play a crucial role in chronic inflammatory processes and appear to determine the nature of the inflammatory response by directing the selective recruitment and activation of inflammatory cells and their survival within the lungs. In vitro studies using macrophage, alveolar, and bronchial epithelial cells, have shown that ROS increase gene expression of inflammatory mediators such as IL-1 and TNF-α. Direct or indirect oxidative stress to the airway epithelium and alveolar macrophages may also generate cytokines such as TNF-α, which in turn can activate airway epithelial cells. The proinflammatory genes, e.g. TNF-α, IL-8, IL-1, iNOS, COX-2, ICAM-1, IL-6, GM-CSF, stress response genes (HSP-27, 70, 90 and heme oxygenase-1), and antioxidant enzymes (γ-glutamylcysteine synthetase or γ-GCS, MnSOD, thioredoxin) are induced. The genes for these inflammatory mediators are regulated by redox-sensitive transcription factors such as NF-kB and AP-1.

**Antioxidant protective gene expression**

An important effect of oxidative stress and inflammation is the upregulation of protective antioxidant genes. Amongst antioxidants, GSH and its redox enzymes appear to have an important protective role in the lung. Oxidative stress causes upregulation of γ-glutamylcysteine synthetase, an enzyme involved in the synthesis of GSH, as an adaptive mechanism against subsequent oxidative stress. It was found that expression of γ-GCS mRNA is elevated in the lungs of smokers and is even more pronounced in those with COPD. Important protective antioxidant genes such as genes for MnSOD, γ-GCS, heme oxygenase-1 (HO-1), glutathione peroxidase (GPx), thioredoxin reductase, and metallothionein are induced by various oxidative stresses, including hypero-
Roles of ROS in signal transduction

ROS have been implicated in the activation of transcription factors such as NF-κB and AP-1, and in the signal transduction and gene expression involved in cellular inflammatory actions. Both environmental and inflammatory cell-derived ROS can lead to activation and phosphorylation of the mitogen-activated protein kinase (MAPK) family, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 kinase, and phosphatidylinositol-3 kinase (PI-3K), via the sensitive cysteine-rich domain. Activation of the sphingomyelinase-ceramide pathway also occurs leading to increased gene expression. This eventually results in the regulation of distinct proinflammatory and antioxidant genes involved in several cellular events, including apoptosis, cell proliferation, transformation, and differentiation.(29)

It is hypothesized that oxidation of sulfide groups in signaling proteins causes structural modifications, resulting in the exposure of active sites and consequent protein activation. Such molecular targets include transcription factors (NF-κB, AP-1), signaling molecules such as ras/rac or JNK, protein tyrosine phosphatases, and p21ras. Thiol molecules such as intracellular GSH and thioredoxin are of central importance in regulating such redox signaling pathways, by reducing disulfide bridges or oxidized cysteine residues.(29,32)

Damage occurs at special positions of the p53 gene, called mutation hot spots, which have been previously linked with cigarette smoke. An attached methyl group provides an environment that attracts the carcinogens to these sites where they then react and cause mutations. It has been reported that a particular carcinogen binds to normal guanine, without this methyl group, and the bulky chemical carcinogen resides at an external binding site and changes in shape completely. It assumes an intercalated structure in which the carcinogenic residue is sandwiched between adjacent base pairs in the double helix.

Apoptotic mechanism related to smoking and COPD

Smoking is considered the major cause of COPD. All smokers develop airway inflammation through oxidative stress with macrophages, neutrophils, lymphocytes, eosinophils, NK-cells and the mediators involved. Through the activation of NF-κB, macrophages release proinflammatory mediators, lymphocyte chemotactic agents and elastolytic enzymes, and activate neutrophil driven serine proteases and GM-CSF. Neutrophils release IL-8, which in turn recruits neutrophils to the airways. In response to cigarette smoke, lung epithelium may release TNF-α, TGF-β, IL-1β, GM-CSF, IL-8 and ROS. An increased number of lymphocyte T CD8+ and CD4+ subpopulations may lead to lung epithelium cell apoptosis and necrosis through perforins and granzyme-B, and TNF-α activation. Moreover, increased expression of IL-6, IL-10, IL-12, IL-13, and IFN-γ is observed. It is possible to target new treatment strategies such as: agents directed against adhesion molecules, chemokines, phosphodiesterase 4, p38 MAPK, NF-κB, PI-3Kγ, TGF-β, NO synthase, serine proteases and matrix metalloproteinases.(33)

COPD is characterized by chronic inflammation of the airways and progressive destruction of lung parenchyma, a process that in most cases is initiated by cigarette smoking. Several mechanisms are involved in the development
of the disease: (1) influx of inflammatory cells into the lung (leading to chronic inflammation of the airways), (2) imbalance between proteolytic and anti-proteolytic activity (resulting in the destruction of healthy lung tissue), (3) oxidative stress, and (4) apoptosis of structural cells in the lung. There is an increase in apoptotic alveolar epithelial and endothelial cells in the lungs of COPD patients. Since there is no counterbalance by an increase in the proliferation of these cells, the net result is destruction of lung tissue and the development of emphysema. Vascular endothelial growth factor (VEGF) plays a pivotal role in the induction of apoptosis of structural cells in the lung. Caspase-3 and ceramide are also mediators of apoptosis and could be targets to prevent it.\(^{34,35}\)

**Smoking and sperm apoptosis in the male reproductive system**

It was found in smokers that the intensive expression of phosphatidylserine (PS) on the sperm plasma membrane surface assay was detected by annexin V positive staining. There was a significant increase in the population of apoptotic spermatozoa in the ejaculates of smokers. DNA damage (high frequencies of double- and single-stranded DNA breaks) in spermatozoa of smokers is increased when compared to non-smokers. Sperm DNA integrity of healthy smokers remains in the normal range, but a clear negative trend is observed, especially in respect to disturbance of plasma membrane phospholipid asymmetry.\(^{36}\) ROS play an essential role in the pathogenesis of many reproductive processes. In male-factor infertility, oxidative stress attacks the fluidity of sperm plasma membrane and the integrity of DNA in the sperm nucleus. Reactive oxygen species induced by DNA damage may accelerate the process of germ cell apoptosis, leading to a decline in sperm counts associated with male infertility. ROS mediated female fertility disorders share many pathogenic similarities with the ones on the male side. These similarities include a potential role in the pathophysiology of endometriosis and unexplained infertility. High follicular fluid ROS levels are associated with negative \textit{in vitro} fertilization (IVF) outcomes, particularly in smokers. Moreover, oxidative stress may be responsible in hydrosalpingeal fluid mediated embryotoxicity as well as poor \textit{in vitro} embryonic development. High levels of ROS are detrimental to the fertility potential both in natural and assisted conception states.\(^{37}\)

**Smoking and placenta in pregnancy**

Smoking during pregnancy perturbs maternal hemostasis via activated coagulation, which could include greater coagulation (fibrin-type fibrinoid deposition) in the placental intervillous space. This might affect intervillous hemodynamics and transport of oxygen and nutrients to the fetus. Fibrin deposits could influence the sizes and numbers of intervillous spaces (pores), and perivillous fibrin could reflect changes in the nature or activity of trophoblast. The total surfaces of syncytial knots decline in smokers and the surfaces of syncytial bridges increase. This is associated, particularly in heavy smokers, with reduced deposits of perivillous fibrin at syncytial knots. In all placentae, the greatest deposits occur where there is trophoblast denudation. Little fibrin is seen on thin regions of syncytiun. Regardless of smoking status, intervillous fibrin reduces intervillous pore size and increases pore numbers. However, heavy smokers have larger pores. Reductions in syncytial knots are consistent with reports that smoking reduces the incidence of
trophoblast apoptosis, while increases in syncytial bridges are consistent with enhanced branching angiogenesis. Results confirm that perivillous fibrin accumulates preferentially at denudation sites. They are also suggested that smoking perturbs the normal pattern of fibrin deposition, the impact is greater in heavy smokers and the placental site is privileged in terms of fibrinolytic or anti-coagulatory activity. This activity seems to reside in thin regions of syncytium.(38)

The human placental syncytiotrophoblast undergoes apoptosis, and this process is associated with inhibition of pregnancy by the smoking habit. In the same way that the presence of trophoblast apoptosis is associated with modifications of the maternal-fetal exchange, the inhibitory effect of the smoking habit on syncytiotrophoblast could be responsible for the poor prognosis of pregnancy in the presence of maternal smoking.(39)

Smoking and low back pain

Cigarette smokers have an increased risk of low back pain, which may be caused by disc degeneration and spinal instability. Ischemia, apoptosis, faulty synthesis of disc macromolecules, and an imbalance between disc matrix proteinases and their inhibitors may be involved in the pathogenesis of disc degeneration. Along with degeneration, the primary avascular disc turns vascular. There is some evidence that disc degeneration in cigarette smokers is more severe than that in non-smokers. Cigarette-smoking increases serum proteolytic activity by releasing proteolytic enzymes from neutrophils in alveolar capillaries, and inhibiting the activity of α-1 antiprotease, the most potent protease inhibitor. The high serum proteolytic enzymes of cigarette-smokers accesses to a previously degenerated neovascularized disc and speed up the degenerative process, resulting in spinal instability. (40)

Role of β-carotene on apoptosis in smokers

Human intervention trials have suggested that supplemental β-carotene results in more cancer in smokers, whereas it is a protective in non-smokers. However, the mechanisms underlying these effects are still unknown.

Many studies suggest a protective role of β-carotene against cancer. However, many trials have shown that β-carotene increases the incidence of lung cancer in heavy smokers and asbestos workers. To explain this paradox, it can be hypothesized that β-carotene modulates intracellular redox status and, through this mechanism, it affects redox-sensitive molecular pathways involved in the regulation of cell cycle progression and apoptosis. At low concentrations, the carotenoid may serve as an antioxidant, inhibiting free radical production, while at relatively high concentrations and/or in the presence of a chronic oxidative stress (i.e. smoke), it may behave as a prooxidant, propagating free radical-induced reactions, consuming endogenous antioxidants and inducing DNA oxidative damage. In this context, it may regulate cell growth and death by the modulation of redox-sensitive genes and transcription factors. (41)

In RAT-1 fibroblasts, tar caused increased 8-hydroxy-2’-deoxyguanosine (8-OHdG), and this effect was enhanced by the concomitant presence of β-carotene in a dose- and time-dependent manner. Fibroblasts treated with tar alone decreased their cell growth with respect to control cells through an arrest of cell cycle progression in the G0/G1 phase and an induction of apoptosis. These effects were
accompanied by an increased expression of p53, p21 and Bax, and a decreased expression of cyclin D1. In contrast, fibroblasts treated with tar and β-carotene, after an initial arrest of cell growth at 12 hours, re-entered the cell cycle and were unable to undergo apoptosis at 36 hours. Concomitantly, after the p53 expression had increased at 12 hours, it progressively returned to basal levels at 36 hours by a mechanism independent of Mdm2. It was followed by a decrease in p21 and Bax expression, and an increase in cyclin D1 expression. During tar treatment, a depletion of β-carotene was also observed in the fibroblasts. Moreover, the presence of the carotenoid remarkably enhanced cyclooxygenase-2 expression induced by tar.(42) Carotenoid ability in inhibiting or enhancing apoptosis depends on several factors: carotenoid concentration, concerted action of multiple micronutrients, cell type, and redox status.(43)

Concluding remarks

Smoking is a major factor for oxidative stress, and its cessation should be recommended to everybody in order to prevent or slow down the progression of COPD, atherosclerosis, degenerative diseases, infertility and spine instability. There is evidence of apoptosis involved in many cells such as endothelial cells, placental syncytiotrophoblasts, fibroblasts, and spermatozoa in smokers evaluated extensively in both in vitro and in vivo models. Antioxidant supplementation is advisable to non-smokers and especially smokers to prevent and inhibit disease progression and cancer development by nutritional means.

References

การตายแบบอะพอพโทสิสเกิดขึ้นในคนสูบบุหรี่และโรคปอดเรื้อรัง

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