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Review article

TOBACCO SMOKING, OXIDATIVE STRESS AND CANCER: A REVIEW

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ABSTRACT

Tobacco smoke contains mutagenic chemicals that are in the "probably carcinogenic" or "possibly carcinogenic" categories. In addition to free radicals, cigarette smoke is also rich in combustion toxic gases that can reach a very high concentration and become involved in more radical formation. Tobacco smoke contains a mixture of chemicals, including a host of reactive oxygen species (ROS), among others, that can damage cellular and sub-cellular targets, such as lipids, proteins, and nucleic acids. A growing body of evidence supports a key role for smoking-induced ROS and the resulting oxidative stress in inflammation and carcinogenesis. Smoking is one of the causes of the incidence and mortality of cancer in the world. This study aimed to review the relationship between smoking and especially the use of cigarettes with common cancers of various organs of the body. In addition to free radicals, cigarette smoke is also rich in combustion toxic gases that can reach a very high concentration and become involved in more radical formation. Smoking increases the risk of cancers of the lungs, bladder, cervix, kidney, larynx (voice box), pharynx (upper throat), nose, mouth, oesophagus (foodpipe), pancreas, stomach, liver and some types of leukaemia. Within this review article we will focus on the correlation between smoking and oxidative stress and the role of smoking in increasing the risk of cancer.

Introduction

Tobacco smoking (TS) is one of the causes of the incidence and mortality of cancer in the world [1]. It is responsible for about 25% of all cancers in men, 4% of all cancers in women and about 16% of all cancers in both sexes in most developed countries and 10% in less developed countries [2]. In the United States, approximately 40% of the cancers diagnosed is related to tobacco consumption [3]. According to recent research evidence, tobacco causes a lot of cases of lung cancer [4]. It is the leading cause of cancers of oral and throat, vocal cords, esophagus, stomach, kidneys, pancreas, liver, bladder, cervix, colon and rectum, and types of leukemia [2] [5] [6] [7] [8]. According to the Center for Cancer Prevention (CDC), tobacco-related cancers have been diagnosed between 2008 and 2013 for some 660000 people in the United States, but 343,000 of these people have died [9-10].

Tobacco smoke contains a complex mixture of chemicals, including a host of reactive oxygen- and nitrogen species (ROS and RNS), among others, that can damage macromolecular targets, such as lipids, proteins, and nucleic acids. Accumulating evidence shows an important role for smoking-induced ROS and the resulting oxidative stress in inflammation and cancer. This review article centers on elucidating the interconnections among smoking, oxidative stress, inflammation, and cancer by highlighting the macromolecular damage that occurs consequent to exposure to smoke-derived/induced ROS. A focal point of the article is the vicious cycle in which smoking-related oxidative stress causes inflammation, which in turn, results in further generation of ROS, and potentially increased oxidative damage to macromolecules that may trigger carcinogenesis. We note that there is a distinction between oxidation response elicited by 'direct' smoke-derived ROS and the response stimulated by 'indirect' smoke-induced ROS. It is important to distinguish the former from the latter as the direct oxidative damage by free radicals and ROS present in cigarette smoke may be less pronounced than the indirect damage/response triggered by other toxicants and carcinogens in the smoke, e.g., aldehydes or particulate matter, or their secondarily formed metabolites (see, Section 7). In addition, it is worth mentioning that cigarette smoke contains a wide variety of carcinogenic compounds, many of which exert their effects through mechanisms that do not involve oxidative damage [1, 11–14]. We acknowledge that there is a wealth of information on smoking-induced ROS and oxidative stress in humans, animal models, and in vitro cell culture systems [15–17]. We should, however, emphasize that the objective of this review is to showcase representative studies, but by no means, discuss the existing literature (in its entirety), to establish the interplays among smoking, oxidative stress, inflammation, and cancer.

Tobacco smoke is divided into the mainstream (smoker inhaled) and the sidestream smoke. The mainstream is divided into a particulate solid phase (tar) and the gas phase (toxic gases, volatile organic compounds, VOCs, free radicals, etc.). Cigarette tar

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contains remarkably high concentrations of stable free radicals (ca. 1017 spins·g−1) with very long lifetimes. The sidestream smoke is divided in the solid and gas phases, containing higher concentrations of toxic and carcinogenic compounds and other volatile and semivolatile compounds [7–9]. Free radicals and oxidants in the gas phase exist in a steady state in which they are continuously formed and destroyed and their concentration increases as the smoke ages [10, 11]. The gas phase is around 0.4–0.5 g/cigarette and contains ca. 500 volatile organic and inorganic compounds [12]. The particulate phase (tar) consists of fine and very fine particles (0.1–1.0 μm, aerodynamic diameter) penetrating deep into the alveoli. Some of the water-soluble components of aqueous cigarette tar (ACT) can produce superoxide anion (O2•−) and subsequently H2O2 and the reactive hydroxyl radical (HO•), which cause oxidative damage to cellular membrane lipids, proteins, enzymes and DNA [13, 14]. The sidestream smoke consists of similar chemical components in the solid and gas phases and is also rich in highly reactive and short-lived free radicals. Passive smoking (or environmental tobacco smoke, ETS) has been proved to be a health hazard for non-smokers and its burden of major lung diseases [15]

CARCINOGENIC COMPOUNDS IN TOBACCO SMOKE

The International Agency for Research on Cancer (IARC) has classified carcinogens into 4 categories, including Classes 1, 2A, 2B, and 3 [12,13]. Class 1 carcinogens are known to cause cancer in humans. Class 2A carcinogens are most likely to cause cancer in humans, whereas Class 2B agents could possibly be carcinogenic in humans. Class 3 comprises compounds for which carcinogenicity data are limited [14]. To decipher the role of smoking in cancer development, it is important to understand what carcinogenic compounds are produced when a cigarette is smoked [13-15]. Tobacco smoke contains more than 7,000 chemicals, of which nearly 70 have been identified as known or suspected carcinogens (see, Table 1) [12]. For example, benzo[a]pyrene (B[a]P), a PAH compound found in tobacco smoke, is causally linked to lung cancer development , whereas 4-aminobiphenyl, a primary smoke-derived aromatic amine, is a well-known bladder carcinogen . Moreover, free radicals originating from tobacco smoke are implicated in the etiology of many subtypes of oral cancer, as they induce a state of chronic inflammation that is considered a common feature of oral carcinogenesis (see, next section) [1, 16- 17].

Analytical chemistry studies have demonstrated that incomplete combustion of organic compounds in tobacco results in the formation of a wide range of carcinogens, such as PAHs and aromatic amines [1,18]. Also, heat-associated degradation of certain tobacco constituents gives rise to various carcinogenic compounds [1]. For example, propylene glycol, which is used as a tobacco additive (serving as humectant), undergoes heat degradation to form propylene oxide, a Class 2B carcinogen [1, 11]. Another group of carcinogens found in tobacco smoke is N-nitrosamines [1]. Several tobacco-derived N-nitrosamines are among the most potent chemical carcinogens [12]. There are multiple varieties of N-nitrosamines, including volatile nitrosamines (VNAs) and TSNAs. These chemicals can be found naturally in tobacco leaves in limited quantities, but concentrations increase during the processing and curing of tobacco, as well as during its pyrolysis, i.e., when tobacco is smoked [12]. Yield of VNA and TSNA compounds also depends on the blend of tobacco . Blends with higher nitrate levels produce more nitric oxide during smoking than blends with lower nitrate amounts [1]. Nitric oxide is quickly oxidized to form nitrogen dioxide which, along with other nitrogen oxides, reacts with amines and nicotine to produce VNAs and TSNAs, respectively [1, 12]. Many TSNAs generated through these reactions, such as N'-nitrosonornicotine (NNN) and 4-(methy1nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are known human carcinogens (i.e., Class 1 carcinogens) [1, 12]. Oxidation can also lead to the production of ethylene oxide, a Class 1 carcinogen, through the reaction of oxygen and ethene in tobacco smoke.

TABLE -1 SELECTED KNOWN OR SUSPECTED CARCINOGENS IN MAINSTREAM CIGARETTE SMOKE.

Chemical family	Compound	Quantity per cigarette	IARC carcinogen class
Polycyclic aromatic hydrocarbons	Benzo[*a*]pyrene	8.5–17.6 ng	1
	Benz[*a*]anthracene	20–70 ng	2A
	Dibenz[*a,h*]anthracene	4 ng	2A
	Benzo[*b*]fluorathene	4–22 ng	2B
	Benzo[*j*]fluorathene	6–21 ng	2B
	Benzo[*k*]fluorathene	6–12 ng	2B
	Dibenzo[*a,l*]pyrene	1.7–3.2 ng	2B
	Dibenzo[*a,e*]pyrene	Present	2B
	Indenol[1,2,3-*cd*]pyrene	4–20 ng	2B
	5-methylchrysene	U-0.6 ng	2B
Heterocyclic compounds	Benzo [*b*]furan	Present	2B
	Dibenz[*a,h*]acridine	U-0.1 ng	2B
	Dibenz[*a,j*]acridine	U-10 ng	2B
	Dibenzo[*c,g*]carbazole	U-0.7 ng	2B
	Furan	20–40 μg	2B
Aromatic amines	2-naphthylamine	1–22 ng	1
	4-aminobiphenyl	2–5 ng	1
	2-toluidine	30–200 ng	2A
	2,6-dimethylaniline	4–50 ng	2B
Organic compounds	Vinyl chloride	11–15 ng	1
	Ethylene oxide	7 μg	1
	Acrylamide	Present	2A
	Acetamide	38–56 μg	2B
	Acrylonitrile	3–15 μg	2B
	1,1-dimethylhydrazine	Present	2B
	Propylene oxide	U-100 ng	2B
	Urethane	20–38 ng	2B
Phenolic compounds	Caffeic acid	< 3 μg	2B
	Catechol	59–81 μg	2B
Inorganic compounds	Radioisotope polonium-210	0.03–1.0 pCi	1
	Hydrazine	24–43 ng	2B
Chemical family	**Compound**	**Quantity per cigarette**	**IARC carcinogen class**
N-nitrosamines	*N*-nitrosonornicotine	154–196 ng	1
	4-(methy1nitrosamino)-1-(3-pyridyl)-1-butanoe	110–133 ng	1
	N-nitrosodimethylamine	0.1–180 ng	2A
	N-nitrosodiethylamine	U-25 ng	2A
	N-nitrosoethylmethylamine	U-13 ng	2B
	N-nitrosopyrrolidine	1.5–110 ng	2B
	N-nitrosopiperidine	U-9 ng	2B
	N-nitrosodiethanolamine	U-36 ng	2B
Heterocyclic aromatic amines	3-amino-3-methylimidazo[4,5-*f*]quinoline	0.3 ng	2A
	2-amino-9H-pyrido[2,3-*b*]indole	25–260 ng	2B
	2-amino-3-methyl-9H-pyrido[2,3-*b*]indole	2–37 ng	2B
	3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole	0.3–0.5 ng	2B
	3-amino-1-methyl-5H-pyrido[4,3-*b*]indole	0.8–1.1 ng	2B
	2-amino-6-methylpyrido[1,2-a:3',2'-*d*]imidazole	0.37–0.89 ng	2B
	2-aminodipyrido[1,2-a:3'2'-d]imidazole	0.25–0.88 ng	2B
	2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine	11–23 ng	2B
Metals	Arsenic	40–120 ng	1
	Beryllium	0.5 ng	1
	Nickel	U-600 ng	1
	Chromium (hexavalent)	4–70 ng	1
	Cadmium	41–62 ng	1
	Lead (inorganic)	34–85 ng	2A
	Cobalt	0.13–0.20 ng	2B
Nitro compounds	Nitromethane	0.5–0.6 μg	2B
	2-nitropropane	0.7–1.2 ng	2B
	Nitrobenzene	25 μg	2B
Volatile compounds	Benzene	12–50 μg	1
	1,3-butadiene	20–40 μg	2A
	Isoprene	450–1,000 μg	2B
Aldehydes	Formaldehyde	10.3–25 μg	1
	Acetaldehyde	770–864 μg	2B

FREE RADICALS IN TOBACCO SMOKE

Free radicals are atoms, molecules, or ions that are unstable, redox active, and highly reactive toward cellular and sub-cellular targets as they contain unpaired electrons [14-19,20]. Free radicals are by-products of natural reactions occurring in the body, including metabolic processes and immune system response. Exogenous sources of free radicals include substances present in the air we breathe, the food we eat, and the water we drink [17, 19]. Environmental and lifestyle factors, such as cigarette smoking, represent major sources of exogenous free radical exposures to humans [20, 21]. Free radicals can damage cellular structure, e.g., cell membrane, or macromolecules, e.g., proteins, lipids, and nucleic acids, through a process involving abstraction of their electrons [16-18,20]. This process is called "oxidation", and the induced damage is termed "oxidative damage" [16-23].

Tobacco smoke is comprised of mainstream smoke (MS) and sidestream smoke (SS), both of which carry large quantities of free radicals. MS is generated when taking a puff from a cigarette, and is inhaled directly from the filter/cigarette end into the oral cavity and down to the respiratory tract [14,15]. SS is formed by the burning of a cigarette from the lit end, and is produced in-between puffs. Both MS and SS can be partitioned into two phases according to the size of their constituents [14]. The two phases include tar (particulate) and gas phases [15]. The tar phase consists of compounds, which are 0.1–1 micrometers (μm) in diameter (average=0.2 μm), and the gas phase comprises chemicals with a diameter smaller than 0.1 μm [15]. Both the gas and tar phases of tobacco smoke contain huge amounts of free radicals; for example, the gas phase delivers upwards of 1015 free radicals with every puff inhaled, and tar, per gram, gives rise to nearly 1017 free radicals. These free radicals are carbon-, nitrogen-, and oxygen-centered radical species, such as semiquinone, hydroxyl, and superoxide radicals [1. The small oxygen- and carbon-centered radicals in the gas phase are much more reactive than the tar-phase free radicals [1]

OXIDATIVE STRESS: SMOKE-INDUCED ROS AND CANCER

ROS comprise both free radical and non-free radical oxygen intermediates, such as hydrogen peroxide (H2O2), superoxide (O2•−), singlet oxygen (1O2), and the hydroxyl radical (•OH) [16-17]. ROS are generated as a byproduct of the aerobic metabolism of oxygen and play key roles in homeostasis and cell signaling. ROS are also involved in other metabolic processes and immunity, e.g., via the nicotinamide adenine dinucleotide phosphate oxidase (NADPH) pathway . In addition, ROS are produced by phagocytic cells, such as neutrophils, eosinophils, and mononuclear phagocytes (e.g., macrophages) in response to stressors [21]. The formation of ROS can also be stimulated by a variety of exogenous agents, including pollutants, dietary agents, drugs, lifestyle factors, or radiation. Substantial quantities of ROS are produced in the mitochondria as a natural by-product of oxidative phosphorylation, which generates adenosine triphosphate (ATP). ATP is used as an energy source for most cellular functions, including active transport and cell signaling [25]. Production of ATP occurs mainly through aerobic respiration using the electron transport chain (ETC) mechanism [25]. ETC operates through the transfer of electrons from one complex to another via redox reactions, and ends with oxygen as the final electron acceptor [26]. Cells acquire large quantities of ATP through this process; however, due to electron leak, ETC can also result in the production of a wide range of ROS [26]. The generated ROS can directly or indirectly damage cellular and sub-cellular targets, thus resulting in adverse biological consequences. Cells have evolved elaborate antioxidant defense mechanisms to counteract the effects of ROS [26-29]. However, external factors, e.g., environment, can impose an additional burden of ROS on the cells, thus overloading the antioxidant defense system and disrupting the homeostasis between oxidants and antioxidants [29]. This imbalance is known as "oxidative stress", a condition in which the amount of ROS exceeds the capacity of the antioxidant system within an organism [26]. In humans, environmental exposure and lifestyle factors, specifically cigarette smoking, are prominent sources of oxidative stress [26-29,30].

Oxidative stress can induce both apoptosis (programmed cell death) and cellular senescence (a state of permanent growth arrest without undergoing apoptosis) [31-33]. Whether a cell undergoes apoptosis or senescence depends on the severity of damage and the tissue type; however, both events act as protective mechanisms to prevent damaged cells from proliferating [34]. This is to avoid genomic instability and propagation of the induced damage to progeny cells. Upon evasion of apoptosis or senescence, however, oxidative stress and the excess ROS in the cell can further damage macromolecular targets, such as proteins, lipids, and nucleic acids [22,27,30-38]. The induced damage to these macromolecules is significant because maintaining the integrity of DNA/RNA, proteins, and lipids is critical to determining the health vs. disease state. Accumulating evidence supports a major role for oxidative stress in the development of a variety of human diseases, including cancer [22]. Because genomic instability is a hallmark of cancer, the ROS that damage DNA, are of special importance in carcinogenesis [17]. Whilst the critical ROS comprise O2•−, H2O2, •OH, 1O2, the latter two are of most significance because they can directly attack and damage DNA . Although O2•− and H2O2 are not as reactive as •OH and 1O2, they are abundant by-products of aerobic metabolism, and can undergo Haber-Weiss reactions with iron to generate •OH . Thus, a buildup of O2•− and H2O2 is still a major contributor to the accumulation of oxidative DNA damage because both of these two ROS can be converted to •OH which, in turn, can inflict damage on DNA [16-17].

Both the gas and tar phases of tobacco smoke yield large quantities of ROS [18]. ROS in the gas phase are generated during the combustion of tobacco, and are inhaled by the smoker as part of the mainstream smoke [14]. The tar phase contains several relatively stable free radicals, such as a quinone/hydroquinone (Q/QH2) complex held in the tarry matrix [18]. This Q/QH2 polymer may function as an active redox system by reducing molecular oxygen in the smokers' lungs to produce O2•−, which can eventually form other free radicals, such as H2O2 and •OH [18,19]. It is important to recognize the distinction between ROS that are derived 'directly' from tobacco smoke and those that are formed 'indirectly' (e.g., from other toxicants or carcinogens or their secondarily formed metabolites) as they may impose distinct burden of oxidative stress and/or elicit different biological responses (see, below). Importantly, oxidative stress resulting from the gas- or tar-phase derived ROS can be augmented by a defect or saturated antioxidant defense system, or as a consequence of additional ROS or other reactive metabolites generated through biotransformation of tobacco smoke chemicals inhaled by smokers [28].

As particulates from tobacco smoke are deposited into the lungs, a layer of tar begins to accumulate. This forms an aqueous

ENDOGENOUS SOURCES OF ROS

ROS are produced from molecular oxygen as a result of normal cellular metabolism. ROS can be divided into 2 groups: free radicals and nonradicals. Molecules containing one or more unpaired electrons and thus giving reactivity to the molecule are called free radicals. When 2 free radicals share their unpaired electrons, nonradical forms are created. The 3 major ROS that are of physiological significance are superoxide anion (O2 2.), hydroxyl radical (_OH), and hydrogen peroxide (H2O2). ROS are summarized in Table 2. Superoxide anion is formed by the addition of 1 electron to the molecular oxygen. This process is mediated by nicotine adenine dinucleotide phosphate [NAD(P)H] oxidase or xanthine oxidase or by mitochondrial electron transport system. The major site for producing superoxide anion is the mitochondria, the machinery of the cell to produce adenosine triphosphate. Normally, electrons are transferred through mitochondrial electron transport chain for reduction of oxygen to water, but approximately 1 to 3% of all electrons leak from the system and produce superoxide. NAD(P)H oxidase is found in polymorphonuclear leukocytes, monocytes, and macrophages. Upon phagocytosis, these cells produce a burst of superoxide that lead to bactericidal activity. Superoxide is converted into hydrogen peroxide by the action of superoxide dismutases (SODs, EC 1.15.1.1). Hydrogen peroxide easily diffuses across the plasma membrane. Hydrogen peroxide is also produced by xanthine oxidase, amino acid oxidase, and NAD(P)H oxidase [39,40] and in peroxisomes by consumption of molecular oxygen in metabolic reactions. In a succession of reactions called Haber–Weiss and Fenton reactions, H2O2 can breakdown to OH2 in the presence of transmission metals like Fe21 or Cu21 [45] and can damage proteins, lipids, and carbohydrates and DNA. It can also start lipid peroxidation by taking an electron from polyunsaturated fatty acids. Granulocytic enzymes further expand the reactivity of H2O2 via eosinophil peroxidase and myeloperoxidase (MPO). In activated neutrophils, H2O2 is consumed by MPO. In the presence of chloride ion, H2O2 is converted to hypochlorous acid (HOCl). HOCl is highly oxidative and plays an important role in killing of the pathogens in the airways.28 However, HOCl can also react with DNA and induce DNA–protein interactions and produce pyrimidine oxidation products and add chloride to DNA bases[44,45]. Eosinophil peroxidase and MPO also contribute to the oxidative stress by modification of proteins by halogenations, nitration, and protein cross-links via tyrosyl radicals [46-49] Other oxygen-derived free radicals are the peroxyl radicals (ROO$_). Simplest form of these radicals is hydroperoxyl radical (HOO$_) and has a role in fatty acid peroxidation.

Free radicals can trigger lipid peroxidation chain reactions by abstracting a hydrogen atom from a sidechain methylene carbon. The lipid radical then reacts with oxygen to produce peroxyl radical. Peroxyl radical initiates a chain reaction and transforms polyunsaturated fatty acids into lipid hydroperoxides. Lipid hydroperoxides are very unstable and easily decompose to secondary products, such as aldehydes (such as 4-hydroxy-2,3-nonenal) and malondialdehydes (MDAs). Isoprostanes are another group of lipid peroxidation products that are generated via the peroxidation of arachidonic acid and have also been found to be elevated in plasma and breath condensates of asthmatics[49-54]. Peroxidation of lipids disturbs the integrity of cell membranes and leads to rearrangement of membrane structure. Hydrogen peroxide, superoxide radical, oxidized glutathione (GSSG), MDAs, isoprostanes, carbonyls, and nitrotyrosine can be easily measured from plasma, blood, or bronchoalveolar lavage samples as biomarkers of oxidation by standardized assays.

TABLE 1. Major Endogenous Oxidants

Oxidant	Formula	Reaction Equation
Superoxide anion	$O_2^{\cdot-}$	$NADPH + 2O_2 \leftrightarrow NADP^+ + 2O_2^{\cdot-} + H^+$ $2O_2^{\cdot-} + H^+ \rightarrow O_2 + H_2O_2$
Hydrogen peroxide	H_2O_2	Hypoxanthine + $H_2O + O_2 \rightleftarrows$ xanthine + H_2O_2 Xanthine + $H_2O + O_2 \rightleftarrows$ uric acid + H_2O_2
Hydroxyl radical	•OH	$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {\cdot}OH$
Hypochlorous acid	HOCl	$H_2O_2 + Cl^- \rightarrow HOCl + H_2O$
Peroxyl radicals	ROO•	$R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$
Hydroperoxyl radical	$HOO^{\cdot}$	$O_2^{\cdot-} + H_2O \rightleftarrows HOO^{\cdot} + OH^-$

Exogenous Source of Oxidants

Cigarette Smoke

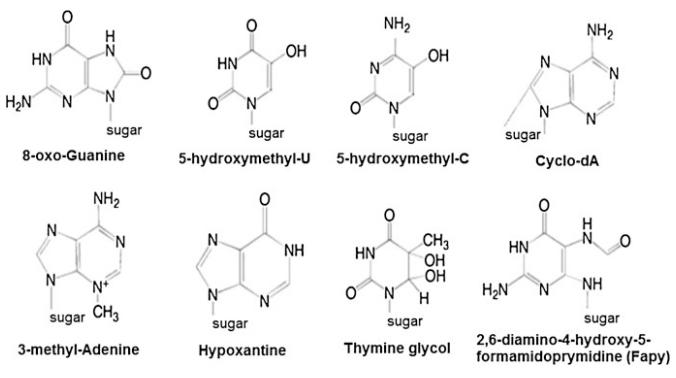
Cigarette smoke contains many oxidants and free radicals and organic compounds, such as superoxide and nitric oxide.36 In addition, inhalation of cigarette smoke into the lung also activates some endogenous mechanisms, such as accumulation of neutrophils and macrophages, which further increase the oxidant injury.

EFFECTS OF OXIDATIVE STRESS DAMAGE TO DNA

ROS can lead to DNA modifications in several ways, which involves degradation of bases, single- or doublestranded DNA breaks, purine, pyrimidine or sugar-bound modifications, mutations, deletions or translocations, and cross-linking with proteins. Most of these DNA modifications (Fig. 1) are highly relevant to carcinogenesis, aging, and neurodegenerative, cardiovascular, and autoimmune diseases.

Tobacco smoke, redox metals, and nonredox metals, such as iron, cadmium, chrome, and arsenic, are also involved in carcinogenesis and aging by generating free radicals or binding with thiol groups. Formation of 8-OH-G is the bestknown DNA damage occurring via oxidative stress and is a potential biomarker for carcinogenesis. Promoter regions of genes contain consensus sequences for transcription factors. These transcription factor–binding sites contain GC-rich sequences that are susceptible for oxidant attacks. Formation of 8-OH-G DNA in transcription factor binding sites can modify binding of transcription factors and thus change the expression of related genes as has been shown for AP-1 and Sp-1 target sequences.103 Besides 8-OH-G, 8,59-cyclo-29-deoxyadenosine (cyclo-dA) has also been shown to inhibit transcription from a reporter gene in a cell system if located in a TATA box.104 The TATA-binding protein initiates transcription by changing the bending of DNA. The binding of TATA-binding protein may be impaired by the presence of cyclo-dA.

FIGURE 1. Base modifications introduced by reactive oxygen species.



Oxidative stress causes instability of microsatellite (short tandem repeats) regions. Redox active metal ions,hydroxyl radicals increase microsatellite instability. Even though single-stranded DNA breaks caused by oxidant injury can easily be tolerated by cells, double-stranded DNA breaks induced by ionizing radiation can be a significant threat for the cell survival. Methylation at CpG islands in DNA is an important epigenetic mechanism that may result in gene silencing. Oxidation of 5-MeCyt to 5-hydroxymethyl uracil (5-OHMeUra) can occur via deamination/oxidation reactions of thymine or 5-hydroxymethyl cytosine intermediates. In addition to the modulating gene expression, DNA methylation also seems to affect chromatin organization. Aberrant DNA methylation patterns induced by oxidative attacks also affect DNA repair activity.

DNA damage induced by smoking-associated oxidative stress can be efficiently repaired by specialized DNA repair enzymes (see, next section) . However, when not repaired properly, oxidative DNA damage can undergo erroneous replication and lead to mutation [55]. Functionally-important mutations in key genes involved in, e.g., cell growth, differentiation, and survival, are of most relevance to cancer [56,57,58]. Specifically, DNA damage-driven mutagenesis in distinct genomic loci may activate normally inactive protooncogenes or inactivate otherwise active tumor suppressor genes, thereby giving rise to cancer development [57, 59]. Mutations in the TP53 gene are the most frequent genetic alteration in human cancer. Over half of all human cancers harbor mutations in the TP53 tumor suppressor gene. Inactivating mutations in the TP53 gene have been observed in nearly all types of smoking-associated cancer [59,60]. Have reported inactivating mutations in the TP53 tumor suppressor gene in lung tumors of current and former smokers, with the majority of mutations being G:C T:A transversions at known lung cancer mutational 'hotspots', including codons 157, 158, 245, 248, and 273 [58]. This mutational fingerprint is considered a 'smoking signature', which has been ascribed to tobacco smoke constituents, such as PAHs and specific ROS [50-58]. We note that many chemicals in a mixture, such as tobacco smoke, induce similar type(s) of mutation, e.g., both ROS and B[a]P (a prototype PAH), give rise predominantly to G:C T:A transversion [55,58 - 64]. Thus, it is a formidable challenge to tease out the contribution of each chemical to the induced mutation spectrum in cells exposed in vitro/in vivo to complex mixture of chemicals, such as tobacco smoke [60-65].

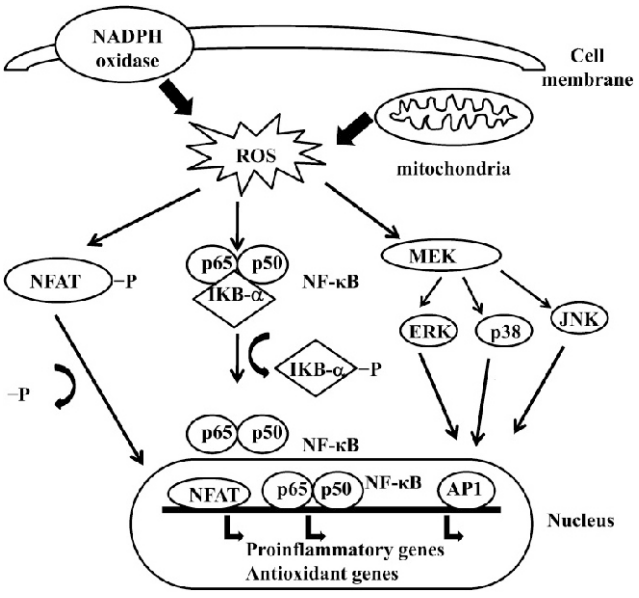
Furthermore, recent work in our laboratory has shown down regulation of the tumor suppressor genes notch receptor 1 (NOTCH1) and HECT and RLD domain containing E3 ubiquitin protein ligase 2 (HERC2) in healthy smokers as compared no nonsmokers [61]. Lack of NOTCH1 is associated with the development of head and neck cancer, comprising malignancies in the oral cavity, nasal cavity, paranasal sinuses, pharynx, and larynx [62,63], and a dysfunctional HERC2 gene has been observed in colorectal and gastric cancers [64]. Recently, Ogawa et al. [65] have demonstrated that treatment of the human airway basal stem cells with cigarette-smoke extract resulted in increased KRAS and RAS protein family activation in vitro. Consistent with this finding, they also observed that airway epithelial cells brushed from healthy smokers had elevated RAS activation compared to nonsmokers [65]. The protooncogene K-RAS is one of the three human RAS genes (other members: H-RAS and N-RAS) that are among the most frequently mutated genes in human cancer [66]. Activating mutations in the RAS protooncogenes have been found in 20–25% of all human cancers, including lung, colon, and breast cancers, and up to 90% of certain types of tumors, e.g., pancreatic cancer [66,67].

EFFECTS OF OXIDATIVE STRESS ON SIGNAL TRANSDUCTION

ROS can induce expression of several genes involved in signal transduction[68,69]. A high ratio for GSH/GSSG is important for the protection of the cell from oxidative damage. Disruption of this ratio causes activation of redox sensitive transcription factors, such as NF-kB, AP-1, nuclear factor of activated T cells and hypoxia-inducible factor 1 , that are involved in the inflammatory response. Activation of transcription factors via ROS is achieved by signal transduction cascades that transmit the information from outside to the inside of cell. Tyrosine kinase receptors, most of the growth factor receptors, such as epidermal growth factor receptor, vascular endothelial growth factor receptor, and receptor for platelet-derived growth factor, protein tyrosine phosphatases, and serine/threonine kinases are targets of ROS [69-70]. Extracellular signal-regulated kinases, JNK, and p38, which are the members of mitogen-activated protein kinase family and involved in several processes in cell including proliferation, differentiation, and apoptosis, also can be regulated by oxidants. Under oxidative stress conditions, cysteine residues in the DNA-binding site of c-Jun, some AP-1 subunits, and inhibitory k-B kinase undergo reversible S-glutathiolation. Glutaredoxin and TRX have been reported to play an important role in regulation of redox-sensitive signaling pathways, such as NF-kB and AP-1, p38 mitogen-activated protein kinase, and JNK [70-75]

NF-kB can be activated in response to oxidative stress conditions, such as ROS, free radicals, and UV irradiation[74]. Phosphorylation of IkB frees NF-kB and allows it to enter the nucleus to activate gene transcription[75]. A number of kinases have been reported to phosphorylate IkBs at the serine residues. These kinases are the targets of oxidative signals for activation of NF-kB[76]. Reducing agents enhance NF-kB DNA binding, whereas oxidizing agents inhibit DNA binding of NF-kB. TRX may exert 2 opposite actions in regulation of NF-kB: in the cytoplasm, it

Figure 2. Effects of oxidatives stress on singal transduction in the cell.



blocks degradation of IkB and inhibits NF-kB activation but enhances NF-kB DNA binding in the nucleus[77]. Activation of NF-kB via oxidation-related degradation of IkB results in the activation of several antioxidant defense–related genes. NF-kB regulates the expression of several genes that participate in immune response, such as IL-1b, IL-6, tumor necrosis factor-a, IL-8, and several adhesion molecules.142,143 NF-kB also regulates angiogenesis and proliferation and differentiation of cells.

AP-1 is also regulated by redox state. In the presence of H2O2, some metal ions can induce activation of AP-1. Increase in the ratio of GSH/GSSG enhances AP-1 binding while GSSG inhibits the DNA binding of AP-1.144 DNA binding of the Fos/Jun heterodimer is increased by the reduction of a single conserved cysteine in the DNA-binding domain of each of the proteins [80-81] while DNA binding of AP-1 can be inhibited by GSSG in many cell types, suggesting that disulphide bond formation by cysteine residues inhibits AP-1 DNA binding[82,83]. Signal transduction via oxidative stress is summarized in Figure 2.

CONCLUSIONS

Cigarette smoke is a heterogeneous aerosol, which contains more than 4000 chemical. These include various compounds, which are capable of causing an increase in the generation of various reactive oxygen species like , H2O2, , ROO·. These reactive oxygen species in turn are capable of initiating and promoting oxidative damage in the form of lipid peroxidation. Cigarette smoking may thus be associated with an increase in the incidence and severity of various diseases like gastric cancer, chronic obstructive lung disease and Atherosclerosis .

Cigarette contains some of the same poisons (toxins) and cancer causing agents (carcinogens) as does cigarette smoke but in higher concentrations. Cigarette tobacco has a high concentration of nitrogen compounds during fermentation and smoking these compounds give rise to several tobacco specific nitrosamines (TSNA's). The higher concentration of nitrogen oxides, ammonia, carbon monoxide and tar all very harmful. Nicotine is the substance in tobacco that causes addiction.

Each puff of a cigarette contains ~1014 free radicals in the tar phase and ~1015 in the gas phase. In addition to high concentrations of oxides of nitrogen, smokers also have increased phagocyte activities, and are therefore under a high and sustained free radical load. It is thus not surprising that smokers have an increased incidence of diseases associated with oxidative stress. It has been hypothesized that many of the adverse effects of smoking may result from oxidative damage to critical biologic substances. Such damage could result both from oxidants present in cigarette smoke and from the activation of phagocytic cells that generate reactive oxygen species. Oxidative inactivation of antiproteases may be involved in the development of chronic obstructive modification of DNA and can lead to the development of cancer. Tobacco smoke contains a host of ROS that are main determinants of oxidative stress. Oxidative stress is a key contributor to both cancer and inflammatory diseases. Smoking-induced ROS can damage macromolecular targets. Smoking-elicited inflammatory response may generate further ROS/macromolecular damage.

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