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Oxidative stress and oxidative damage in chemical carcinogenesis☆

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ABSTRACT

Reactive oxygen species (ROS) are induced through a variety of endogenous and exogenous sources. Overwhelming of antioxidant and DNA repair mechanisms in the cell by ROS may result in oxidative stress and oxidative damage to the cell. This resulting oxidative stress can damage critical cellular macromolecules and/or modulate gene expression pathways. Cancer induction by chemical and physical agents involves a multi-step process. This process includes multiple molecular and cellular events to transform a normal cell to a malignant neoplastic cell. Oxidative damage resulting from ROS generation can participate in all stages of the cancer process. An association of ROS generation and human cancer induction has been shown. It appears that oxidative stress may both cause as well as modify the cancer process. Recently association between polymorphisms in oxidative DNA repair genes and antioxidant genes (single nucleotide polymorphisms) and human cancer susceptibility has been shown.

Introduction

Cancer induction by chemicals involves a multi-stage, multi-step process. While this process includes multiple molecular and cellular events to transform a normal cell to a malignant neoplastic cell, evidence in recent years has defined at least three steps in the chemical carcinogenesis process (Klaunig and Kamendulis, 2004). These steps have been identified as initiation, promotion and progression (Fig. 1). Initiation is the step where the normal cell undergoes unrepaired DNA damage and DNA synthesis to produce a mutated, initiated cell. The production of the initiated cell can occur through interaction with physical carcinogens such as UV light and radiation as well as chemical carcinogens that possess DNA damaging or mutagenic properties (genotoxic agents). In addition, recent evidence has shown that during cell proliferation, mutations may be acquired through misrepair of damaged DNA resulting in spontaneous initiated, mutated cells. Following the formation of the initiated cell, chemicals as well as endogenous physiological compounds can cause the selective clonal growth of this initiated cell through the process of tumor promotion. Tumor promotion involves the expansion of the initiated cell to a focal lesion. The tumor promotion process is not a direct DNA reactive or damaging process, but involves modulation of gene expression that results in the increase in cell number through cell division and/or decrease in apoptotic cell death (Klaunig and Kamendulis, 2004). Following continual cell proliferation additional mutations may be acquired in the preneoplastic cells resulting in the production of neoplasms. A third step, progression, involves additional damage to the genome, and unlike the promotion step, is irreversible. This multi-step process has been well defined in rodent systems and evidence has shown that similar processes occur in primates including humans.

The mechanisms by which carcinogens induce their effects have been studied extensively for over a half a century. Using the rodent liver model as an example, the modes of action by which carcinogens induce hepatic cancer can be placed in several categories based upon molecular target and cellular effects (see Table 1). These include genotoxicity and non-genotoxicity, including cytotoxicity, receptor interaction and mitogenic effects.

It is well documented that some agents can induce oxidative stress through either an increase reactive oxidative species generation from endogenous or exogenous sources or a decrease in antioxidant capabilities and oxidative DNA repair (Klaunig and Kamendulis, 2004). In viewing the role that oxidative stress may play in multi-stage process, it is apparent that oxidative DNA damage can have mutagenic effects and result in the formation of the initiated cell during this process. In addition, oxidative stress can modulate the redox potential of the cell and modify gene expression and thus participate at the tumor promotion phase of the cancer process (Benhar et al., 2002). The impact of endogenous as well as exogenous sources of ROS on the cell that if not handled by antioxidants can result in an increase in oxidative stress in the cell. This oxidative stress then, in turn, may damage critical macromolecules resulting in chromosome instability, genetic mutation and/or modulation of cell growth that may result in cancer.

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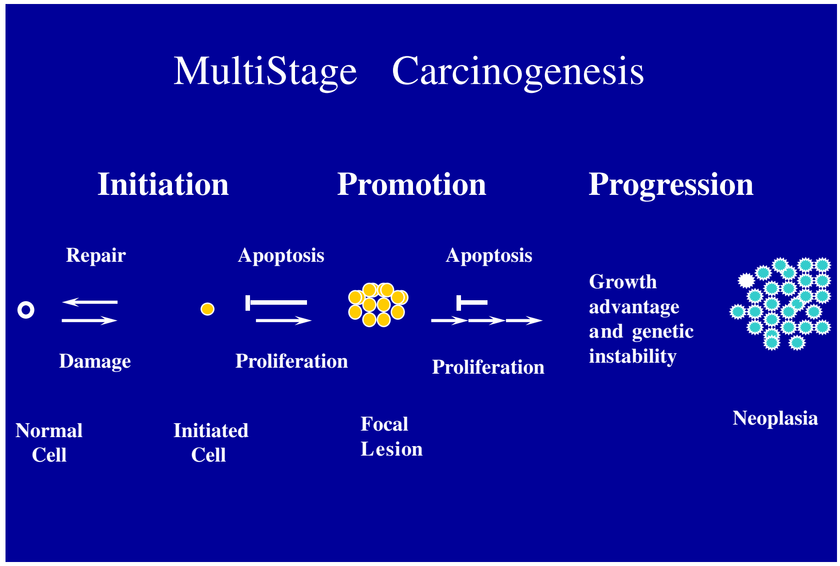

Fig. 1. Multistage carcinogenesis.

Sources of ROS

Experimental evidence indicates critical roles of ROS in tumor development (Guyton and Kensler, 1993; Petros et al., 2005; Ishikawa et al., 2008; Kumar et al., 2008). While the exact mechanisms of ROS production and human cancer development have not been fully defined, it is known that ROS can be produced from both endogenous and exogenous sources. Endogenous sources include mitochondria, peroxisomes, and inflammatory cell activation (Klaunig and Kamendulis, 2004). A wide array of exogenous sources is also documented in the literature, including environmental agents, radiation, therapeutic agents, and tobacco smoke (Table 2).

Exogenous generation of ROS

ROS may arise from several external sources including ionizing radiation and xenobiotics. Ionizing radiation can cause damage to living cells including DNA damage and gene mutation, cell death, and cancer (Riley, 1994). Most of the toxic effects of ionizing radiation are mediated by ROS (Tulard et al., 2003). ROS are generated rapidly through radiolysis of water molecules, as well as from secondary reactions leading to increased levels of ROS, which can persist and diffuse within the cell resulting in delayed toxic effects (Riley, 1994; Leach et al., 2001). Ionizing radiation is a proven carcinogen in humans and has been shown to induce cancer in multiple target organs.

Table 1
Modes of action (MOA) of rodent hepatic carcinogens.

Genotoxicty
Cytotoxicity
Receptor mediated
PPAR alpha (peroxisome proliferator)
CAR
Estrogen
Ah
Mitogenic
Oxidative stress
Porphyria
Metal overload (Cu Fe)
Increase in target cell number
(increased cell proliferation/decreased apoptosis)
P450 induction

Xenobiotics including environmental agents also have been shown to generate ROS in cells either metabolizing directly to primary radical intermediates or by activating endogenous sources of ROS (Rice-Evans and Burdon, 1993; Klaunig et al., 1997). The induction of oxidative stress and damage has been observed following exposure to xenobiotics of varied chemical structures and modes of action (Table 2). Chlorinated compounds, radiation, metal ions, barbiturates, phorbol esters, and some peroxisome proliferating compounds are among the classes of compounds that have been shown to induce oxidative stress and oxidative damage in vitro and in vivo (Klaunig et al., 1997).

Endogenous cellular generation of ROS

The well established endogenous sources of ROS include mitochondria, peroxisomes, and inflammatory cell activion (Klaunig and Kamendulis, 2004). The mitochondria are the major source of ROS in the cell. Since it was first reported by Loschen et al. (1971) that mitochondria generate superoxide radicals, extensive studies have been conducted to elucidate the mechanism of mitochondrial ROS generation and the physiological and toxicological significance of the mitochondrial ROS. Interest in mitochondrial bioenergetics and biogenesis and mitochondrial ROS has been renewed in recent years, linking mitochondrial ROS to tumor development (Gottlieb and Tomlinson, 2005; Guzy et al., 2008; Ishikawa et al., 2008). However, the role of ROS in tumor development and progression is still controversial, largely due to the fact that the exact mechanisms of mitochondrial ROS generation are not fully defined. It has been known that ROS production in mitochondria is species and tissue and cell cycle specific (Ku et al., 1993; Sohal et al., 1995). In addition, more ROS is produced in mitochondria from aging cells compared to younger counterparts (Ku et al., 1993), and in general higher in cancer cells than normal cells (Trachootham et al., 2006). The biological significance of these differences of mitochondrial ROS generation remains defined.

The ROS produced are by-products of mitochondrial oxidative phosphorylation. It is estimated that during mitochondrial respiration, 1–2% of electrons released from electron transfer chain (ETC) to form superoxide, although this value is controversial (St-Pierre et al., 2002). The major sites are defined to be mitochondrial complex I, NADH–ubiquinone oxidoreductase, and complex III, the ubiquinol–cytochrome c oxidoreductase, both responsible for much of superoxide production in mitochondria.

Table 2
Environmental and pharmaceutical carcinogens that can induce oxidative stress and damage.

Chemicals	Experimental models	ROS or effects	Reference
Genotoxic			
N-nitroso compounds	Murine	MDA, 8OHdG	(Bartsch et al., 1989; Srinivasan and Glauert, 1990; Chung and Xu, 1992)
Bisphenol A	Rats	8OHdG	(Cho et al., 2009)
BaP	Mice	8OHdG	(Mauthe et al., 1995)
AFB-1	Rats	8OHdG	(Shen et al., 1995)
Heterocyclic amines	In vitro	·OH	(Sato et al., 1992)
MMC and 2-acetylaminofluene	In vitro	·OH	(Komiyama et al., 1982; Srinivasan and Glauert, 1990)
KBrO3	Rats	8OHdG	(Umemura et al., 1995)
Nongenotoxic			
2-Butoxyethanol	Mice		(Siesky et al., 2002)
Acrylonitrile	Rats; in vitro	MDA, 8OHdG	(Whysner et al., 1998; Kamendulis et al., 1999; Pu et al., 2009)
Chlorinated compounds (TCDD, dieldrin, DTT, lindane)	Murine; in vitro	lipid peroxidation, $O2^{\bullet -}$, etc.	(Videla et al., 1990; Junqueira et al., 1991; Alsharif et al., 1994)
Phenobarbital	Murine	·OH, 8OHdG, lipid peroxidation	(Junqueira et al., 1991)
Metal (nickel, BrCl, chromium, Fe-NTA iodobenzene)	Murine	·OH, 8OHdG, MDA, NO	(Klein et al., 1991; Sai et al., 1992; Bagchi and Stohs, 1993; Iqbal et al., 1995)
Peroxisome proliferator (DEHP, WY-14643, clofibrate, ciprofibrate, PFDA)	Murine	·OH, 8OHdG, etc.	(Srinivasan and Glauert, 1990; Tamura et al., 1990; Wada et al., 1992; Cattley and Glover, 1993; Huang et al., 1994)
CCl4		Trichloromethyl peroxyl radical	(Brattin et al., 1985)
Phorbol ester (TPA, PMA)	Murine, in vitro	·OH, 8OHdG	(Witz, 1991)
Quinones	V79 cells	8OHdG	(Dahlhaus et al., 1995)

The mechanism of ROS generation at mitochondrial complex III has been well characterized, which involves in the ubiquinone cycle of complex III (Betteridge, 2000). The mitochondrial complex III-dependent ROS generation has been implicated in cancer development and progression in recent studies. For example, hypoxia plays a causal role in pathological progression of cancer. It has been suggested that ROS generated at the ubiquinone cycle of complex III regulates hypoxic activation of hypoxia-inducible factors (HIFs), a family of transcription factors, including a broad range of cellular functions including cell proliferation and angiogenesis which is implicated in tumor development an progression (Bell et al., 2007). Mitochondrial complex I is the other site for ROS production. ROS generation at mitochondrial complex I has also been implicated into the mechanism of cancer progression (Ishikawa et al., 2008; Koshikawa et al., 2009; Sun et al., 2009). In addition, mitochondrial complex II, succinate: ubiquinone oxidoreductase, has been demonstrated to be another source of ROS production in mitochondria, which receives increasing attention in relation to tumorigenesis (Yankovskaya et al., 2003; Gottlieb and Tomlinson, 2005; Guzy et al., 2008).

Peroxisomes are another important cellular source of ROS generation. These cellular organelles consume oxygen to generate hydrogen peroxide and superoxide. The production of ROS involves a battery of peroxisomal oxidases including acyl-CoA oxidase and xanthine oxidase (see review; Schrader and Fahimi, 2006), which generate hydrogen peroxide and superoxide. The amount of oxidases and H_2O_2 produced varies among cells and tissues. In rat liver, peroxisomes produce about 35% of all H_2O_2 which accounts for about 20% of total oxygen consumption (Schrader and Fahimi, 2006). Although antioxidant enzymes such as catalase, glutathione peroxidase (Asayama et al., 1994), copper zinc superoxide dismutase (Dhaunsi et al., 1992), epoxide hydrolase, and peroxiredoxin I (Immenschuh et al., 2003) are present in peroxisomes, peroxisomes still contribute to a net-production of cellular ROS. Induction of peroxisomal ROS has been suggested to be implicated in chemical induced carcinogenesis. Peroxisome proliferators including hypolipidemic drugs, phthalate esters and halogenated solvents all lead to tumor development (Reddy et al., 1980; Reddy et al., 1983; Moody et al., 1991). Although a causal link has not been established between peroxisome proliferator-induced ROS and tumorigenesis (Rose et al., 1999), ROS has been associated with liver tumor induction (Klaunig and Kamendulis, 2004).

Inflammatory cells including neutrophils, eosinophils, and macrophages are an additional endogenous source of ROS and contribute significantly to the cellular ROS load. These phagocytes produce ROS using NADPH oxidase, a complex composed of two membrane bound subunits gp91phox and p22phox, and three regulatory cytosolic components $p47^{pho}x$, $p67^{phox}$, and Rac (Babior, 1999). Upon activation by a variety of endogenous and exogenous stimuli, phagocytes undergo a respiratory burst leading to transient increase in oxygen uptake resulting in generation of ROS through NADPH oxidase that catalyzes the one electron reduction of oxygen, using NADPH as the electron donor (Griendling et al., 2000). The O_2^- generated in this reaction can be further dismutated by superoxide dismutase to hydrogen peroxide. These reactive oxidative species play an important role in killing bacteria. Besides acting as cellular defense mechanism, recent studies suggest that these phagocyte-dependent ROS may also be involved in the development of a variety of cancers. However, it should be noted here, NADPH oxidase is not unique to inflammatory cells, it also presents in other non-phagocytes particularly in vascular cells. The importance of NADPH oxidase is increasingly being recognized in cancer cells as well. In a study on regulation of angiogenesis Xia et al. (2007) found that knockout of NADPH oxidase subunit $p47^{phox}$ diminishes ROS generation leading to decreased expression of VEGF and HIF-1α and tumor angiogenesis, indicative of critical role of endogenous ROS produced by NADPH oxidase in tumorigenesis.

Kupffer cells, the resident macrophages of the liver, have been increasingly recognized in the role of hepatocarcinogenesis. It has been well documented that the Kupffer cell oxidant production is critically involved in peroxisome proliferator-induced neoplasia (Rose et al., 1999). Mechanistic studies suggest that the Kupffer cell may be involved in the promotion stage of carcinogenesis since activation of Kupffer cells with LPS resulted in an increase in focal volume and DNA synthesis within diethylnitrosamine-induced hepatic foci, whereas inactivation of Kupffer cells using dietary glycine ablated the LPS-induced effects on liver cell growth (Klaunig and Kamendulis, 2004).

Interaction of ROS and biological macromolecules

Lipid peroxidation

Polyunsaturated fatty acids (PUFA), containing two or more double bonds, are readily oxidized by ROS to produce lipid peroxyl radicals and lipid hydroperoxides, a process called lipid peroxidation (Rice-Evans and Burdon, 1993). Once the process of lipid peroxidation is initiated, it proceeds as a free radical-mediated chain reaction involving initiation, propagation, and termination (Gago-Dominguez et al., 2005). Initiation of lipid peroxidation is started by the abstraction of hydrogen atom from polyunsaturated fatty acid moiety of membrane phospholipids by the attack of reactive species (Gago-Dominguez et al., 2005). The fatty acid radicals formed in the initiation step will react with the neighboring lipid molecules and generate new free radicals. The propagation phase can repeat many times until it is stopped by chain breaking antioxidants (Rice-Evans and Burdon, 1993; Foy, 1999; Niki et al., 2005).

The breakdown of lipid peroxidation products results in the formation of many reactive aldehydes, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) (Tuma, 2002). These aldehydes have shown reactivity with protein and DNA and form adducts with these macromolecules (Kikugawa et al., 1987; Nicholls et al., 1992; Uchida and Stadtman, 1993; Klaunig et al., 1998). MDA and MDA-MDA dimmers are mutagenic (Spalding, 1988; Klaunig and Kamendulis, 2004).

Isoprostanes, prostaglandin like compounds, are generated from the free radical-initiated peroxidation of arachidonic acid (Morrow et al., 1990; Liu et al., 1999; Morrow and Roberts, 2002). They are formed in vivo and can be detected in plasma, tissue and urine, and are elevated by oxidative stress inducers such as chloroform, carbon tetrachloride, and cigarette smoking (Morrow et al., 1995; Kadiiska et al., 2005a; Kadiiska et al., 2005b; Delannoy et al., 2009).

Oxidative DNA damage

Oxidative DNA damage is a major source of the mutation load in living organisms (Lu et al., 2001). Over 100 oxidative DNA adducts have been identified (von Sonntag, 1987; Dizdaroglu, 1992; Demple and Harrison, 1994; Brown et al., 2009). The estimated frequency of oxidative DNA damage is at 10^4 lesions/cell/day in humans (Fraga et al., 1990; Lu et al., 2001). Free radicals can attack both purine and pyrimidine bases, as well as the deoxyribose backbone. ROS-induced DNA damage includes single- or double-strand breakage, base modifications, deoxyribose modification, and DNA cross-link. If DNA damage is not properly repaired prior to or during replication, it may result in cell death, mutation, or induction of transcription, induction of signaling pathways, replication errors, and genomic instability, all of which have been associated with the carcinogenesis process (Marnett, 2000; Cooke, 2003; Klaunig and Kamendulis, 2004; Valko et al., 2006).

Several ROS are capable of producing oxidative DNA damage. Intermediates from the lipid and protein oxidation process may react with DNA and form DNA adducts (Kikugawa et al., 1987; Nicholls et al., 1992; Uchida and Stadtman, 1993; Klaunig et al., 1998; Lu et al., 2001; Tuma, 2002). However, the hydroxyl free radical is considered the major ROS that interacts with DNA bases, deoxyribose and free nucleotides (Lu et al., 2001). The hydroxyl free radical is highly reactive and has short half-life. Thus its migration in the cell is limited and reacts with cellular components quickly in close vicinity (Klaunig and Kamendulis, 2004). Hydrogen peroxide, a precursor to hydroxyl radical, is less reactive and more readily diffusible and thus more likely to be involved in the formation of oxidized bases (Guyton and Kensler, 1993; Barber and Harris, 1994). Peroxynitrite, formed from the reaction of nitric oxide and superoxide, is also diffusible between cells. During inflammation, activated macrophages produce nitric oxide and superoxide, which in turn may give rise to peroxynite and modify DNA bases. This may explain the reported association between inflammation and mutation (Marnett, 2000; Klaunig and Kamendulis, 2004).

There have been at least 24 bases modifications related to ROS attack of DNA that have been identified to date (Wilson et al., 2003). Among these modified bases, 8-hydroxy-2′-deoxyguanosine (8OHdG) is the predominant adduct. 8OHdG is formed through the oxidation of guanine at the C8 position in guanine base (Kasai et al., 1984; Dizdaroglu, 1985). This oxidative DNA adduct has been detected in different tissues and urine and it is the most commonly used biomarker for oxidative DNA damage as well oxidative stress both in vitro and in vivo. A variety of environmental agents have been reported to induced elevated levels of 8OHdG, including ionizing radiation; cigarette smoking; metals such as arsenic, iron, and cadmium; and organic chemicals such as carbon tetrachloride and chloroform (Kasprzak, 2002; Kadiiska et al., 2005a,b). Elevated levels of 8OHdG have also been detected in some disease conditions, including diabetes, Parkinson's disease, Alzheimer's disease, and chronic hepatitis C infection (Owen et al., 1996; Kato et al., 2001; Kakimoto et al., 2002; Moreira et al., 2005).

Oxidative damage to RNA

Compare to oxidative modifications of DNA by ROS, the extent and distribution of oxidative damage to RNA is not as well understood. There is evidence that shows that purified RNA possesses greater oxidative stability than DNA (Thorp, 2000). Parallel experiments on chemical cleavage of DNA and RNA by enediynes and rhodium (III) photoxidants revealed that C-H bond cleavage might be more difficult in RNA than in DNA (Chow et al., 1992; Kappen and Goldberg, 1995; Thorp, 2000). 2-Nitropropane treatments resulted in 3.6-fold increase in 8OHdG in DNA versus 11-fold increase on 8-hydroxyguanosine in RNA in rat liver (Fiala et al., 1989). Administration of oxidant doxorubicin to Fisher-344 rats resulted in a significant increase in liver RNA oxidation, but no significantly increased DNA oxidation (Hofer et al., 2006). Oxidative RNA damage include modifications of bases and ribose, base excision, and strand break (Li et al., 2006). Several oxidative RNA adducts including 8-oxoguanosine, 8-hydroxyadenine, and 5-hydroxycitosine have been reported (Yanagawa et al., 1992; Schneider et al., 1993). Oxidative damage to protein-coding RNA or non-coding RNA may potentially cause errors in protein synthesis or dysregulation of gene expression, and such non-acutely lethal insults to cells might be associated with underlying mechanisms of several human diseases. Oxidative RNA damage has been described in several neurodegenerative diseases (Li et al., 2006; Nunomura et al., 2007).

Oxidative damage to protein

Reactive species can react directly with protein or they can react with sugars and lipids, generating products that in turn react with the protein (Klaunig et al., 1997; Freeman et al., 2009). Within the protein, either the peptide bond or the sidechain may be targeted. Basic mechanisms involved in the oxidation of proteins by ROS were elucidated by studies in which amino acids, peptides, and proteins were exposed to ionizing radiations under conditions where •OH or a mixture of •OH and $O^{2-\bullet}$ are formed (Stadtman, 2004). It has been demonstrated that the attack by hydroxyl free radical leads to an abstraction of a hydrogen atom from the protein polypeptide backbone and form a carbon-centered radical (Stadtman, 2004).

Oxidative damage to proteins ROS may have significant biological consequences. It can result in modification of enzyme activity (stimulation or inhibition) (White et al., 1976; Bellomo et al., 1983). Damage to the membrane transport proteins may produce cellular ionic homeostasis and lead to alterations in intercellular calcium and potassium that will trigger a series of changes in cells (Kerr et al., 1992; Klaunig et al., 1998). Changes to receptor proteins and gap junction proteins may also modify signal transfer in cells. In selective cases alteration of protein structure may allow the target protein to be further attacked by proteinases (Klaunig et al., 1998).

Effects of ROS on DNA mutation

Epidemiological studies indicated that chronic oxidative stresses are strongly associated with carcinogenesis (Hwang and Bowen, 2007). For example, ulcerative colitis has long been linked with high incidence of colorectal cancer, and chronic gastritis, such as HP infection, has been associated with a high incidence of gastric cancer (Seril et al., 2003; Konturek et al., 2006). Oxidative damage and modifications to DNA bases lead to changes in the genomic information. This damage may include point mutations, deletions, insertions, or chromosomal translocations which may cause oncogene activation and tumor suppressor gene inactivation, and potentially lead to initiation of carcinogenesis (Toyokuni, 2006). $P15^{INK4B}$ and $p16^{INK4A}$ tumor suppressor genes have been reported to be the major target gene of ROS-induced renal cell carcinoma in rats (Tanaka et al., 1999). Reports have shown that ROS and oxidative DNA damage may be involved in AFB1-induced *p53* and *ras* gene mutations in hepatocarcinogenesis (Shen and Ong, 1996), and in human skin cancers in sun exposed areas and in UV-induced mouse skin cancers (Nishigori et al., 2004).

In vitro systems have been used to study the mutagenic effects of DNA damage induced by ROS including H_2O_2, $^1O_2$, $O_2^{-\bullet}$, HOC1, and $HO^{\bullet}$. Mutants can be identified phenotypically, and DNA isolated from phage-exhibiting mutant phenotypes is then sequenced, which allow the determination of the frequency and types of mutations within the target gene (McBride et al., 1991). The most frequent mutations that result from ROS-induced damage to DNA in bacteria are C to T transitions (Feig et al., 1994). A tandem CC to TT double substitution has been shown to be induced by ROS generated by a variety of systems.

The most extensively studied, and also the most abundant oxidative DNA lesion produced is 8OHdG, which is highly mutagenic due to mispairing with adenine during DNA replication (Cheng et al., 1992). Numerous studies have demonstrated that the 8OHdG level is elevated in various human cancers (Tanaka et al., 2008; Valavanidis et al., 2009), and in animal models of tumors (Muguruma et al., 2007; Harvilchuck et al., 2009; Pu et al., 2009). These studies strongly supported that oxidative DNA damage is involved in the etiology of cancer. Based on this evidence, 8OHdG has been widely used as a biomarker of oxidative DNA damage, and measurement of 8OHdG level is applied to evaluate the load of oxidative stress (Hwang and Bowen, 2007; Valavanidis et al., 2009). The assessment of oxidative DNA damage products in various biological matrices, such as serum and/or urinary 8OHdG, could be important to understanding the role of oxidative stress and subsequently devising proper intervention strategies. In addition, RNS, produced during the process of chronic inflammation, can cause nitrative DNA damage to form 8-nitroguanine. The formation of 8-nitroguanine has been observed in various human samples, and experimental evidence has suggested that 8-nitroguanine is a mutagenic DNA lesion, which preferentially leads to G→T transversions (reviewed by Kawanishi and Hiraku (2006)). Therefore, 8-nitroguanine could also be used as a potential biomarker to evaluate the risk of inflammation, during which high levels of ROS are usually produced, related carcinogenesis.

Mitochondrial DNA (mtDNA) is more susceptible to oxidation than nuclear DNA (Inoue et al., 2003; Brandon et al., 2006). Evidence exists that oxidative mtDNA damage is involved in the development of many human cancers including colon (Polyak et al., 1998), liver (Nishikawa et al., 2001), breast (Tan et al., 2002), lung (Suzuki et al., 2003), bladder (Chen et al., 2004), prostate (Petros et al., 2005), esophageal cancer (Tan et al., 2006), ovarian (Van Trappen et al., 2007), head and neck (Zhou et al., 2007), and nasopharyngeal (Pang et al., 2008). Mutant mtDNA has been reported to be 220 times more abundant than a mutated nuclear DNA marker of cancer cells (Czarnecka et al., 2006). The mtDNA mutations in cancer could either arise in female germ line (oncogenic germline mutations) and predispose to cancer or arise in the mtDNA of the tissue (tumor-specific mutations) and participate in the tumor progression process (Brandon et al., 2006). mtDNA mutations in tumors generally fall into two main classes: tumorigenic and adaptive. Tumorigenic mtDNA mutations are mutations that inhibit oxidative phosphorylation (OXPHOS) and impede electron flow down the mitochondrial electron transfer chain, resulting in increased ROS production and contribute to cancer promotion and progression. Adaptive mtDNA mutations are milder mutations that facilitate tumor survival under adverse environments (Wallace, 2005; Brandon et al., 2006). It is, therefore, plausible to hypothesize that a positive feedback loop may exist between ROS, mtDNA mutation and tumor development.

ROS effects on gene expression

Most of the effort on examining the effects of ROS has been focused on oxidative DNA damage and mutation; however, the presence of epigenetic effects of ROS has also been examined (Evans et al., 2004). It is well established that upon exposure to oxidants (or oxidative stress-inducing agents), mammalian cells express stress-induced genes, which encode antioxidant defense. Although increases in ROS production may lead to the induction of apoptosis or necrosis, low levels of oxidants, through interaction and modification of genome DNA, may alter gene expression, particularly growth factors and proto-oncogenes (Frenkel, 1992). Researchers investigating the effects of ROS on cell proliferation demonstrated that the induction of cell proliferation occurred only at exposure to low concentrations or transient exposure to ROS (Fiorani et al., 1995). The effect of ROS on cell growth also depends on the cell type; it may promote normal cell proliferation but kill tumor cells (Laurent et al., 2005).

As a signaling messenger, ROS is able to activate critical target molecules such as PKC, which is relevant to tumor progression (Wu, 2006). The effects of cellular oxidants have also been related to activation of downstream transcription factors. The most significant effects of oxidants on signaling pathways have been observed in the nuclear factor erythroid 2-related factor 2 (NF-E2/rf2 or Nrf2) (Kensler et al., 2007), mitogen-activated protein (MAP) kinase/AP-1 (Benhar et al., 2002), and NF-κB pathways (Pantano et al., 2006); hypoxia-inducible transcription factor 1α (HIF-1α) is also activated (Rankin and Giaccia, 2008). The activation of these transcription factors is involved in both cell survival and apoptosis. The cellular concentration of ROS appears to influence the selective activation of these transcription factors and therefore may help explain the observation that either cell death or cell proliferation may result from exposure to oxidative stress.

PKC

PKC (protein kinase C) is a family of serine/threonine kinases that are involved in controlling the function of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues on these proteins. Studies have shown that ROS induces the release of calcium from intracellular stores, resulting in the activation of PKC, that regulates a variety of cell functions including proliferation, cell cycle, differentiation, cytoskeletal organization, cell migration, and apoptosis (Wu, 2006). While PKC can also be activated by ROS (Frank and Eguchi, 2003), the activation of PKC is required for generating ROS in several systems (Lin and Takemoto, 2005). A recent report demonstrated that ROS-mediated sustained activation of PKC signaling pathways plays a critical role in migration of human HepG2 cells (Wu et al., 2006). PKC signaling pathway was also reported to be involved in mitochondrial ROS mediated *HIF-1α* gene activation in lung carcinoma cell line (Koshikawa et al., 2009).

Interestingly, the activation of PKC seems to be differentially regulated by cellular oxidants: oxidation at the NH2-terminal regulatory domain activates PKC, whereas oxidation at the COOH terminal inactivates PKC (Gopalakrishna and Anderson, 1989). Because these pathways regulate cellular mitogenesis, migration, proliferation, survival, and death responses, their aberrant activation has been suggested to be a potential mechanism of ROS-induced carcinogenesis.

Nrf2

Nrf2 is a basic region-leucine zipper (bZip)-type transcription factor, which belongs to cap "n" collar family (Moi et al., 1994) and is located in the chromosome 17q21.3 (Chan et al., 1995). Nrf2 heterodimerizes with members of small Maf family of transcription factors, and then binds to ARE (antioxidant response element), leading to the transcriptional expression of ARE-regulated genes (Itoh et al., 1997). Under basal unstressed conditions, Keap1 (Kelch ECH associating protein 1), a cytosolic repressor protein, binds to Nrf2 and promotes its proteasomal degradation through Cullin 3 (Cul-3)-based E3 ligase (Cullinan et al., 2004). Upon exposure to environmental stressors such as ROS or electrophiles, keap1 undergoes conformational changes, liberating Nrf2 from keap1, Nrf2 then translocates into nucleus to bind to ARE and activate gene transcription (Itoh et al., 1999). The Nrf2-keap1 system has been observed in virtually all vertebrates, including humans, mouse, rats, chicken, and fish, suggesting that Nrf2 is a highly conservative cellular defense mechanism (Kobayashi and Yamamoto, 2006).

The mechanisms for activating of Nrf2 have been intensively investigated since its isolation in 1994 (Moi et al., 1994). A number of stressors including both endogenous and exogenous agents have been reported to activate Nrf2; these stressors included ROS, RNS, lipid aldehydes, 15-dexoy-D12,14-prostaglandin J2, electrophilic xenobiotics and their metabolites (Dinkova-Kostova et al., 2005; Osburn and Kensler, 2007). Recently, Nrf2 was reported to be activated in defending metals, such as chromium (Cr) (VI) (He et al., 2007), and cadmium (Ali et al., 2008; Liu et al., 2009), induced reactive stress by transactivating ARE-driven genes, and reduction of ROS production. Activation of Nrf2 by Cr (VI) was accompanied by the nuclear translocation and deubiquitination of Keap1 indicating the recycling of Keap1 in Nrf2 signaling (He et al., 2007). Two independent mechanisms have been previously demonstrated (reviewed by Osburn and Kensler (2007)) to be responsible for the dissociation of Nrf2 from Keap1: 1) Keap1 contains reactive cysteines (C273 and C288) that form protein–protein crosslinks through intermolecular disulfide bonds upon exposure to electrophiles or oxidant stress; the resulting conformation change leads to the disruption of Keap1–Nrf2 interaction and liberation of Nrf2 (Wakabayashi et al., 2004). 2) Secondary sensor proteins and activation of protein kinases (such as PKC) signaling pathway are involved, resulting in phosphorylation of Nrf2, which enhanced the stability and/or release of Nrf2 from Keap1 (Huang et al., 2002). Most recently, a hypothetic model of Nrf2-mediated redox signaling was brought up (Li and Kong, 2008). In this model, two pools of Nrf2 proteins exist: free floating Nrf2 (fNrf2) and Keap1-binding Nrf2 (kNrf2). Under homeostatic conditions, kNrf2 binds to a Keap1 which destines the Nrf2 proteins to proteasomal degradation, and there is only a small pool of fNrf2, contributing to basal activation. Upon oxidative stress, the conformation change of the Keap1 leads to the inhibition of proteasomal degradation, and Keap1 is saturated by undegraded kNrf2. At the same time, the pool of fNrf2 expands. fNrf2 can sense the change of redox milieu and transmit redox signals to cell nucleus via gradient nuclear translocation. In this model, Keap1 plays a gatekeeper role and dictates the pool size of fNrf2, thus regulating the overall redox sensitivity (Li and Kong, 2008).

The activation of Nrf2 results in transcriptional expression of a broad spectrum of protective enzymes including xenobiotic detoxification, antioxidative response, and proteome maintenance, all favoring cell survival (Kensler et al., 2007). The major antioxidant enzymes have been identified to be including glutathione reductase, peroxiredoxin, thioredoxin and thioredoxin reductase, catalase, copper/zinc superoxide dismutase and glutathione peroxidase (Osburn and Kensler, 2007). Low levels of Nrf2 or loss of Nrf2 activity appear to increase ROS production and DNA damage, and predispose cells to tumorigenesis. For example, disruption of Nrf2 has been shown to increase ROS generation and DNA damage which promote prostate tumorigenesis (Frohlich et al., 2008). Interestingly, emerging data provided evidence that elevated activity may also play a role in the evolution of cancer. Nrf2 and its downstream genes are overexpressed in many cancer cell lines and human cancer tissues, which render cancer cells an advantage for survival and growth (Hayes and McMahon, 2006; Lau et al., 2008). In two separate studies, mutations in Keap1 gene were found to provide a growth advantage for lung cancer cells (Ohta et al., 2008) and breast cancer cells (Nioi and Nguyen, 2007). Biallelic inactivation of Keap1 gene was reported to be a frequent genetic event in non-small cell lung cancer. Loss of function of Keap1 led to constitutive activation of Nrf2-mediated gene expression, favoring the cancer cell survival against chemotherapeutic agents (Singh et al., 2006), suggesting a potential mechanism for chemoresistance in certain cancers.

AP-1

AP-1 protein was first identified as a transcription factor that contributes both to basal gene expression (Lee et al., 1987), as well as phorbol ester (TPA)-inducible gene expression (Angel et al., 1987). Ever since, the gene has been intensively studied. AP-1 is a collection of dimeric bZip proteins that belong to the Jun (c-Jun, JunB, JunD), Fos (FosB, Fra-1, Fra-2), Maf (musculoaponeurotic fibrosarcoma), and ATF (activating transcription factor) subfamilies, all of which can bind TPA or cAMP response elements (Chinenov and Kerppola, 2001). c-Jun, a potent transcriptional regulator, often forms stable heterodimers with Jun proteins, which aid the binding of Jun to DNA (Kouzarides and Ziff, 1988), and is positively autoregulated by its product, Jun/AP-1 (Angel et al., 1988). AP-1 activity is induced in response to H_2O_2 as well as several cytokines and other physical and chemical stresses. In addition, in vitro transcriptional activity of AP-1 is regulated by the redox state of a specific cysteine 64 located at the interface between the two c-Jun subunits, highlighting the importance of redox status on gene transcription (Klatt et al., 1999). The induction of AP-1 by ROS, cytokines, and other stressors is mediated mainly by JNK and p38 MAP kinase cascades (Chang and Karin, 2001). Once activated, JNK proteins translocate to the nucleus and phosphorylate c-Jun and ATF2, enhancing transcriptional activities (Gupta et al., 1995; Karin, 1995). ROS such as H_2O_2 can activate MAP kinases and thereby AP-1 in several manners. One involves the apoptosis signal regulating kinase (ASK1) (Tobiume et al., 2001). Oxidation of thioredoxin, which is an endogenous inhibitor of ASK1, by H_2O_2, resulted in ASK1 activation (Liu et al., 2000; Tobiume et al., 2001). The second mechanism involves oxidant-mediated inhibition of MAP kinase phosphatases, which leads to increased MAP kinase activation. In addition, ROS may activate MAP kinase via PKC pathway (Wu, 2006). Whichever mechanism dominates, activation of MAP kinases directly leads to increased AP-1 activity.

One common effect of AP-1 activation is an increased cell proliferation. In particular, it has been demonstrated that c-fos and c-jun are positive regulators of cell proliferation (Shaulian and Karin, 2001). One of the genes regulated by AP-1 is cyclin D1. AP-1 binding sites have been identified in the cyclin D1 promoter and AP-1 activates this promoter, resulting in activation of cyclin-dependent kinase, which promotes entry into the cell division cycle (Brown et al., 1998). c-Jun also stimulates the progression into the cell cycle both by induction of cyclin D1 and suppression of p21waf, a protein that inhibits cell cycle progression (Bakiri et al., 2000). JunB, considered a negative regulator of c-jun-induced cell proliferation, represses c-jun-induced cyclin D1 activation by the transcription of p16INK4a (Passegue and Wagner, 2000). Although JunD exhibits high sequence homology to c-Jun, its biological consequences of expression and activity are distinct from that of c-Jun (Castellazzi et al., 1991). While most functions of JunD reported so far are related to decrease in cellular oxidative stress. It is recently reported that JunD inhibits intestinal epithelial cell proliferation through the activation of p21 promoter (Li et al., 2002), and reduces tumor angiogenesis by protecting cells from oxidative stress (Gerald et al., 2004). Therefore, the effect of AP-1 activation is dependent on the relative abundance of AP-1 subunits, the composition of AP-1 dimers, cell types, stimuli, as well as cellular environment (Hess et al., 2004).

NF-κB

NF-κB is a nuclear transcription factor that was first identified by Sen and Baltimore (1986). It is ubiquitously expressed and participates in a wide range of biological processes involved in cell survival, differentiation, inflammation, and growth (Sethi et al., 2008). This dimeric transcription factor is composed of different members of the Rel family, consisting of p50 (NF-kB1), p52 (NF-kB2), c-Rel, v-Rel, Rel A (p65), and Rel B (Baeuerle and Baltimore, 1996). Normally, NF-κB dimmers are sequestered in the cytoplasm in an inactive state through binding to inhibitory IkB proteins (IkBa, IkBb and IkBe). Activation of NF-κB occurs in response to a wide spectrum of extracellular stimuli, including cytokines, oxidative stress, oncogenes, and DNA damage, which promote the dissociation of IkBs by sequential phosphorylation and proteolytic degradation, a process that depends on the IkB kinase (IKK) complex, of these inhibitors, thereby allowing the entry of NF-κB into nucleus and binds κB-regulatory elements (Hacker and Karin, 2006; Wu and Miyamoto, 2007). NF-κB has been known to be redox regulated and is a direct target for oxidation that can affect its ability to bind to DNA (Pantano et al., 2006). NF-κB activation has been linked to the carcinogenesis process because of its critical roles in inflammation, differentiation and cell growth (Okamoto et al., 2007). Experimental evidence has demonstrated that NF-κB activation 1) is required for growth factor mediated cell proliferation, 2) promotes tumor cell survival, 3) mediates tumor cell invasion, 4) is needed for angiogenesis, and 5) is involved in tumor cell metastasis (Sethi et al., 2008). It is therefore reasonable that NF-κB serves as a potential molecular target for chemoprevention and therapy (Sarkar and Li, 2008; Shen and Tergaonkar, 2009).

While it is widely accepted that NF-κB is a tumor promoting transcription factor, recent emerging data have suggested an tumor suppressor like effect of NF-κB in carcinogenesis (Chen and Castranova, 2007). As a tumor suppressor, NF-κB functions in DNA repair to preserve genome integrity and senescent state in mouse and human fibroblast senescence models (Wang et al., 2009). Further investigations using different cellular and animal models and human tumor tissues as well are needed to establish the tumor suppressor effect of NF-κB. And caution should also be taken in regard with blocking NF-κB pathway in treating cancers.

HIF-1

HIF-1 is a heterodimeric transcription factor that plays an important role in signaling the cellular oxygen levels. HIF-1 consists of two subunits, HIF-1α (120 kDa) and HIF-1α (91–94 kDa), which belong to the basic-helic-loop-helix (bHLH) proteins of the PAS family. HIF-1α (also known as ARNT) is expressed constitutively in all cells and does not respond to changes in oxygen tension, is essential for hypoxia-induced transcriptional changes mediated by the HIF-1 heterodimer (Wang et al., 1995). The level of HIF-1α is tightly control by the cellular oxygen level. HIF-1α is made continuously and accumulates in hypoxic cells, but is rapidly degraded and is almost absent in normoxic cells. The oxygen-dependent degradation of HIF-1α is sensed by prolyl hydroxylases (PHDs). Following hydroxylation, HIF-1α is then recognized by the von Hippel–Lindau (pVHL, the E3 ubiquitin protein ligase) and subjected to proteasomal degradation (Ivan et al., 2001). Recently, HIF-1α has also been shown to be up-regulated under normal oxygen conditions in response to in response to growth factor (Richard et al., 2000).

HIF-1 has been implicated in the in ROS-induced carcinogenesis in a variety of human tumors, including bladder, breast, colon, glial, hepatocellular, ovarian, pancreatic, prostate, and renal tumors (Talks et al., 2000; Galanis et al., 2008). Elevated HIF-1 expression has been shown to be correlated with poor outcome in patient with head and neck cancer, nasopharyngeal carcinoma, colorectal, pancreatic, breast, cervical, osteosarcoma, endometrial, ovarian, bladder, glioblastoma, and gastric carcinomas (for review, see Rankin and Giaccia, 2008). Taken together, these findings highlight that HIF1 activation is a common event in cancer and suggest that HIF-1 may play a role in tumorigenesis. Emerging evidence indicates that ROS generated by mitochondria are required for stabilization and hypoxic activation of HIF-1α (Simon, 2006; Klimova and Chandel, 2008). Thus, ROS is considered the direct activator of HIF-1 in hypoxic tumors.

Activation of transcription factors is clearly stimulated by signal transduction pathways that are activated by ROS, such as H_2O_2, and other cellular oxidants. Through the ability to stimulate cell proliferation and either positive or negative regulation of apoptosis, transcription factors can mediate many of the documented effects of both physiological and pathological exposure to H_2O_2, or chemicals that induce ROS and/or other conditions that favor increased cellular oxidants. Through regulation of gene transcription factors, and disruption of signal transduction pathways, ROS are intimately involved in the maintenance of concerted networks of gene expression that may interrelate with neoplastic development.

Polymorphisms in oxidative stress related genes

Human genetic variation is very common and single nucleotide polymorphisms (SNPs), which are defined as a variation in a single nucleotide pair which occurs at a population frequency of at least 1%, contribute to the majority of the variants. It is estimated that there are approximately 10 million SNPs in humans (Kruglyak and Nickerson, 2001). While many of these variants are silent (or "neutral") and without functional consequences on gene expression and protein function (Fay et al., 2002), a small portion of these variants are in coding and regulatory region of genes, contribute to the phenotypic change, and are functionally important (Brookes, 1999). The relationship between genetic susceptibility and human cancers has been intensively studied during the last 2 decades, especially after the completion of human genome sequence (Dong et al., 2008). Recent advance in genotyping technologies, for example, the genome wide association studies (GWAS), has led to a rapid increase in available data on common genetic variants and phenotypes and numerous discoveries of new loci associated with risks of human cancers as well as other complex human diseases (Lin et al., 2006; Khoury et al., 2009).

Cancer is a complex disease attributed to the integrated outcome of carcinogen activation or detoxification, DNA repair capacity, and other known or unknown factors. Individual responses to a chemical carcinogenic agent depend on polymorphisms of enzymes responsible for metabolic activation/detoxification of the carcinogen, DNA repair, and apoptosis, as well as promotion and progression in malignantly transformed cells (Belitsky and Yakubovskaya, 2008). In this review, we focus on a panel of oxidative stress related genes that control the levels of cellular ROS and oxidative DNA damage, including genes involved in carcinogen metabolism, antioxidants, and DNA repair pathways. Polymorphisms in these genes may alter the production of ROS and therefore modified risk of cancer.

Polymorphisms in carcinogen metabolizing genes

As has been discussed in the previous section, xenobiotics including various chemical carcinogens can generate ROS either directly through metabolism to primary radical intermediates or indirectly by activating endogenous sources of ROS (Rice-Evans and Burdon, 1993; Klaunig et al., 1997). For example, ethanol is mainly metabolized by CYP2E1 and is known to enhance the activity of this enzyme, leading to a burst of ROS production that damage with consequent toxicity and carcinogenicity in small rodents (Parke, 1994). Aflatoxin B1 (AFB1), a known liver carcinogen, induces ROS production accompanied by its activation via CYP3A4 and /or detoxification via GSTs and EPHX (Shen et al., 1996; Alpsoy et al., 2009). And it has been demonstrated that genetic polymorphisms in these enzymes have been associated with modified liver cancer risk because of AFB1 exposure (McGlynn et al., 2003).

The metabolism of carcinogens has been traditionally categorized into two major phases. Following exposure to a carcinogen, the dominating reactions are mediated by microsomal oxidases encoded by cytochrome P450 (*CYP*) gene superfamily, but other enzymes are included too (Belitsky and Yakubovskaya, 2008). The other enzymes such as epoxide hydrolase 1 (*EPHX1*) use a different chemistry than cytochrome P450. They all use oxygen in some form, mostly from water or molecular oxygen, and generate free chemical groups which can be detoxified through conjugation with phase II enzymes, such as glutathione S-transferase (GST) and N-acetyltransferase-2 (NAT2), into water-soluble chemical groups such as a sugar, amino acid or sulfate molecule. Most of the carcinogen metabolizing genes have been shown to be polymorphic which may alter the activity of an enzyme, and thus, modify individual cancer risk (Hayes et al., 2005; McIlwain et al., 2006; Agundez, 2008; Belitsky and Yakubovskaya, 2008).

CYP constitutes a superfamily of monooxygenases which are responsible for the phase I metabolism of many endogenous as well as exogenous compounds such as drugs and xenobiotic compounds (Lewis et al., 2004). The main CYPs in humans that metabolize carcinogens are CYP1A1, CYP2A6, CYP3A4, CYP1B1, and CYP2E1 (Belitsky and Yakubovskaya, 2008). These enzymes have specificities for various classes of carcinogens and genetic polymorphism has been identified for most of them (Guengerich et al., 1991; Guengerich, 1994; Ingelman-Sundberg, 2004). The individual differences in expression may be due to the genetic polymorphisms or the extent of their induction. Numerous studies have investigated the associations of CYP polymorphisms and many human cancers (Agundez, 2004; Dong et al., 2008).

Glutathione *S*-transferases (GSTs), a major superfamily of dimeric phase II metabolic enzymes, metabolize a variety of environmental carcinogens with a large overlap in substrate specificity. GST enzymes catalyze the conjugation of toxic and carcinogenic electrophilic molecules with glutathione and thereby protect cellular macromolecules against toxic foreign chemicals and oxidative stress (Hayes and Strange, 2000). Human GSTs are divided into three major families, the cytosolic, mitochondrial, and microsomal (now referred to as membrane-associated proteins in eicosanoid and glutathione, MAPEG) (Hayes et al., 2005). Cytosolic GSTs represent the largest family of such transferases and are further divided into eight subclasses: Alpha, Pi, Mu, Omega, Sigma, Theta, Zeta and Kappa, they are all dimeric with subunits of 199–244 amino acids in length (Mannervik et al., 1992; Strange et al., 2001). The chromosomal localization of these genes is reviewed elsewhere (McIlwain et al., 2006). Most of the cytosolic GSTs have been reported to be polymorphic which may contribute to the interindividual difference in response to xenobiotics, and hence distinct cancer risk (Hayes et al., 2005).

Polymorphisms in antioxidant genes

Antioxidant enzymes consist one of the major cellular protective mechanisms against oxidative stress in human body. Malignant transformation may be accompanied by either reduced antioxidant activity or increased levels of ROS (Oberley and Oberley, 1988). Many of the antioxidant genes are known to be polymorphic which lead to altered enzyme activity and regulatory efficiency on ROS level, and finally modify the risk of ROS-induced carcinogenesis. Copper-zinc superoxide dismutase 1 (*CuZnSOD* or *SOD1*) occurs as a dimer of identical 16 KDa subunits. Mutations in *SOD1* have been known to cause 5% of all amyotrophic lateral sclerosis cases (Rosen, 1993). More than 100 mutations have been identified and arise in all five exons of *SOD1* (Andersen et al., 2003). A recent study reported that SNPs in *SOD1* were associated with adult glioma risk (Rajaraman et al., 2009). Several other reports investigated the relationship between common polymorphisms of *SOD1* and risk of breast and prostate cancer, but no significant association was found (Cebrian et al., 2006; Udler et al., 2007).

Manganese superoxide dismutase, MnSOD or SOD2, is a mitochondrial enzyme that catalyzes the formation of H_2O_2 from superoxide radicals generated in human body. The variant allele of *MnSOD* has been associated with elevated risk of breast (Bewick et al., 2008), brain (Rajaraman et al., 2008), prostate (Mikhak et al., 2008), lung (Liu et al., 2004), ovarian (Olson et al., 2004) cancers, and non-Hodgkin lymphoma (Wang et al., 2006).

Superoxide dismutase 3 (SOD3) is a major extracellular antioxidant enzyme expressed in the extracellular matrix of many tissues and especially blood vessels (Marklund, 1984). *SOD3* gene contains three exons with coding region in exon 3. A common genetic variant *SOD(R213G)* with a substitution in the heparin-binding domain was recently reported to be associated with brain tumor (Rajaraman et al., 2008) but not prostate cancer risk (Kang et al., 2007).

Glutathione peroxidase (GPX) is a family of selenium-dependent enzyme with at least four isoenzymes identified so far. GPX is encoded by different genes in various cellular locations. *GPX1*, located on chromosome 3p21.3, is the first identified and the most abundant selenoprotein in mammals (Kiss et al., 1997), and is ubiquitously expressed in humans, protecting cells against oxidative damage by reducing hydrogen peroxide and a wide range of organic peroxides (Arthur, 2000). A SNP with proline–leucine at codon 198 of human *GPX*1 has been identified and associated with many human cancer risks, such as breast (Ravn-Haren et al., 2006), prostate (Arsova-Sarafinovska et al., 2008), lung (Raaschou-Nielsen et al., 2007), and bladder cancer (Ichimura et al., 2004), but are not consistent in all populations (Ahn et al., 2005; Cebrian et al., 2006; Udler et al., 2007).

Glutathione synthase (GS), glutamyl-cysteinyl synthase (GCS) and glutathione reductase (GR) are important enzymes involved in the production and recycling of glutathione; genetic variations in these genes may affect the glutathione levels in human body and thus contribute to oxidative stress (Forsberg et al., 2001a), so it is plausible to hypothesize that changes in these genes may influence cancer risk.

Catalase (CAT) is an endogenous antioxidant enzyme that neutralizes ROS by converting H_2O_2 into H_2O and O_2, and can be up-regulated by oxidative stress (Hunt et al., 1998). A common catalase-262C/T polymorphism has been identified in the promoter region of the human *CAT*, and the variant of this gene affects transcriptional activity and catalase levels in red blood cells (Forsberg et al., 2001b). Because of the importance of this enzyme in regulating ROS levels in human body and the clear role of ROS in tumorigenesis, genetic polymorphisms of this gene are believed to play a role in ROS-induced carcinogenesis. Several epidemiologic studies have investigated the relationship between SNPs of this gene and human cancer risks, however, results remain inconclusive. Polymorphisms of *CAT* was not associated with lung cancer risk in a Chinese population (Ho et al., 2006), non-Hodgkin's lymphoma in the UK (Lightfoot et al., 2006), and prostate cancer in the US (Choi et al., 2007). A recent report suggested that a *CAT* variant allele is associated with a decreased risk of acoustic neuroma (Rajaraman et al., 2008), while this result needs to be confirmed by further investigations.

Polymorphisms in DNA repair genes

As discussed in the previous section, 8OHdG is the most abundant and by far the most intensively studied lesion caused by oxidative stress (Cooke et al., 2003). Several pathways are involved in the removal, or repair, of this lesion from damaged DNA. It is preferentially repaired by base excision repair (BER) enzymes, including 8-oxoguanine DNA glycosylase (OGG1), human endonuclease nei-like glycosylase 1 (NEIL1), and MutY homologue (MUTYH) (Evans et al., 2004). In addition, nucleotide excision repair (NER) may also participate in the process of removing the 8OHdG lesion (Patel et al., 2007). Recently, the human apurinic/apyrimidinic endonuclease (APE1) and xeroderma pigmentosum complementation group C (XPC), a NER pathway enzyme, and NEIL1 proteins have been shown to enhance the activity of OGG1 (Mokkapati et al., 2004; D'Errico et al., 2006; Sidorenko et al., 2007).

hOGG1 (*human 8-oxoguanine DNA N-glycosylase 1 gene*), located at 3p26.2 of the human chromosome, encodes OGG1. Several SNPs within *hOGG1* have been reported (Kohno et al., 1998). Thus, polymorphisms in this gene that alter glycosylase function and an individual's ability to repair oxidatively damaged DNA, possibly resulting in genetic instability that may contribute to carcinogenesis (Boiteux and Radicella, 2000; Ide and Kotera, 2004; Shao et al., 2006). A most frequently found polymorphism is a serine (Ser) to cysteine (Cys) substitution at position 326 of the OGG1 protein. Functional study of this polymorphic enzyme using human cell extracts revealed that cells homozygous for the Cys variant have an almost 2-folder lower 8OHdG DNA glycosylase activity compared with cells with Ser variant (Bravard et al., 2009). Consistent with the enzyme activity, the Cys/Cys cells displayed an increased genetic instability and reduced in vivo 8OHdG repair rates (Bravard et al., 2009). While epidemiologic studies investigating the associations between the SNPs of *OGG1* have led to conflicting results. The variant allele of this *OGG1* was shown to be associated with significantly increased risk a number of human cancers, including lung (Hung et al., 2005; Li et al., 2008), esophageal (Xing et al., 2001), prostate (Xu et al., 2002), and gastric (Farinati et al., 2008) cancer. However, no association was found for polymorphisms of this gene and risk of squamous cell carcinoma of the head and neck (SCCHN) (Zhang et al., 2004), squamous oral carcinomas (Gorgens et al., 2007), and pancreatic cancer (McWilliams et al., 2008). The difference in cancer risks may depend on the exposure of diverse environmental factors (Weiss et al., 2005).

A total of 18 polymorphisms in *APE1* have been reported, among which, *Gln51His* and *Asp148Glu* are the two most common SNPs. Associations between polymorphisms in *APE1* and increased risk of lung, colon, breast, SCCHN, prostate, pancreatic and colorectal cancer have been reported, but with mixed results (Goode et al., 2002; Zhang et al., 2004; Hung et al., 2005; Jiao et al., 2006; Kasahara et al., 2008). SNPs of *MUTYH* gene were also reported and have been associated with risks of lung, colorectum, and head and neck cancer in different populations (Ali et al., 2008; Kasahara et al., 2008; Tao et al., 2008; Miyaishi et al., 2009; Sliwinski et al., 2009). In addition, at least two polymorphic sites for *NEIL1* gene were identified , which may be involved in the pathogenesis of gastric cancer (Shinmura et al., 2004).

Concluding remarks

ROS has been well recognized for playing a dual role as both beneficial and deleterious species (Valko et al., 2007). As discussed in this review, overproduction of ROS via various sources can cause damage to both nuclear and mitochondrial DNA, which have been associated with a number of human cancers. ROS act as secondary messengers in multiple intracellular pathways that confer carcinogenic effects, while ROS can also induce apoptosis and promote cellular senescence, therefore functioning as anticarcinogenic species (Mates et al., 2008). Low levels of ROS involve in cellular defense against infectious agents and ROS-mediated activation of Nrf2 transcriptional expression of antioxidant enzymes protect cells against ROS-induced oxidative stress, a mechanism to re-establish cellular redox homeostasis. Furthermore, individual responses to chemical carcinogens also depend on polymorphisms of enzymes responsible for metabolic activation/detoxification of the carcinogen, producing/reducing ROS, and DNA repair. Future studies should address functional changes of these polymorphic genes and how they are related to cancer risk. Individualized prevention/therapeutic strategy of a cancer should also be developed considering not the specific exposure but also the polymorphism profile of the patient.

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