CHAPTER 8

ROLE OF GENETIC SUSCEPTIBILITY IN ENVIRONMENTAL EXPOSURE INDUCED DISEASES

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Abstract: *Inherited susceptibility* due to a defective gene is a factor in a small percentage of people who develop cancer (<5%), while *induced susceptibility*, which is due to the wide variation in individual responses to exogenous agents, is believed to result from the great diversity in responsiveness to risk factors in the environment. Interindividual variations in DNA repair capacity for specific types of DNA damage are documented. Functional polymorphism has been identified primarily at enzymes associated with redox regulation and detoxification, such as glutathione *S*-transferase and cytochrome p450 isozymes. Cancer susceptibility can be the inability to eliminate mutated cells by apoptosis due to mutation in apoptosis regulatory genes and/or induced disruption in gap junction, activation of proto-oncogene and/or inactivation of suppressive genes. Detectable gene mutations and alterations in signal transduction pathways together with modified post-translational proteins offer valuable molecular biomarkers for occupational and environmental human biomonitoring applied for the identification of potentially hazardous exposures before adverse health effects appear and allow the establishment of exposure limits in order to minimize the likelihood of significant health risks. An emerging concept is that the combined action of environmental factors and individual susceptibility determines an individual's likelihood of developing cancer, asthma, diabetes as well as many other aging-associated diseases.

Introduction

During the last decades diseases such as asthma (Eggleston et al., 1999), obstructive lung diseases (Lagorio et al., 2006) diabetes mellitus (Lee et al., 2006), cardiovascular disease (Chen et al., 2005), cancer (Brennan, 2002) atherosclerosis (Wang and Wang, 2005), Alzheimer's disease (Landrigan et al., 2005) and autoimmune disorders (Dooley and Hogan, 2003) are increasing in incidence. These diseases are multifactorial and all are suggested to involve complex interactions between genetic (individual susceptibility) environmental (potentially modifiable) factors. It is recognized that environmental exposures play a key role factor in their propagation.

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Inherited susceptibility due to a defective gene is a factor in a small percentage of people who develop cancer (<5%). Nearly all hereditary diseases are recessive, meaning that both copies of a gene must be mutated in order for the disease to develop (Risch, 2000). Induced susceptibility, which is due to the wide variation in individual responses to exogenous stressors, is believed to result from the great diversity in responsiveness to risk factors in the environment. These variations, known as polymorphism, are caused by sporadic mutations caused by both endogenous and exogenous processes (Elena and de Visser, 2003). In most instances, such mutations, which result in minor changes in the nucleotide sequence of the coding region as well as 5′ and 3′ untranslated regions, are sufficient to alter expression or stability at both the RNA and protein levels (Malkin, 1995). However, there are many instances, where modifications in gene expression do not involve changes in DNA nucleotide sequences. Modifications in gene expression through methylation of DNA and remodelling of chromatin via histone proteins are believed to be the most important events of the epigenetic changes (Verma and Srivastava, 2002).

Potential sources of susceptibility for complex diseases risk include interindividual variation in DNA repair capacity for specific types of DNA damage (Au et al., 1996). Also variation in enzymes, which activate and detoxify procarcinogens and carcinogens (e.g. Phase I enzymes, which catalyze oxidation, reduction, and hydrolysis reactions, and Phase II enzymes, which catalyze conjugation and synthetic reactions) are causes for interindividual susceptibility. Functional polymorphism has been identified primarily at enzymes associated with redox regulation and detoxification, such as glutathione S-transferase (Nakajima et al., 1995) and cytochrome p450 isozymes (Oyama et al., 1997). Cancer susceptibility can be the inability to eliminate mutated cells by apoptosis due to mutations in the apoptosis regulatory genes (Malkin, 1995), and/or induced disruption in gap junction (Trosko et al., 1994), activation of proto-oncogene (You et al., 1989) and/or inactivation of suppressive genes (Weinberg, 1991; Greenblatt et al., 1994).

BIOLOGICAL VARIABILITY IN THE ACTIVITY OF OXIDANT-PRODUCING ENZYMES

Nitric oxide species (NOS) and reactive oxygen species (ROS) regulate multiple cellular functions such as DNA synthesis (Kandacova and Zagrebel'naia, 2004), signal transduction (Ruiz-Ramos et al., 2005), transcription factor activation, (Bove and van der Vilet, 2006), gene expression (Hsu et al., 2004), cell proliferation (Attene-Ramos et al., 2005) and apoptosis (Nair et al., 2004). Numerous various enzymes including: NADPH oxidase (Fialkow et al., 1994) and xanthine oxidase (Weiss, 1986) generate ROS.

Endothelial cells, neutrophils, macrophages and other inflammatory cells generate and release ROS and NOS via an NADPH-oxidase-dependent mechanism that is mediated by membrane receptor activation of protein kinase C and phospholipase C (Cemerski, 2002; Gelinas et al., 2002). One of the major functions of these free radicals is immunological host defence, where they are generated by macrophages and neutrophils and play critical role as bactericidal, antiviral and anti-tumour agent (Wiesman and B. Halliwell, 1996; Guzik et al., 2003). H_2O_2 is considered to activate NF-κB (Siebenlist et al., 1994), which regulates the expression of multiple immune and inflammatory molecules. Generation of such ROS to a level that overwhelms tissue antioxidant defence systems, results in an oxidative stress, whose magnitude depends on the ability of the tissues to detoxify such free radicals (Ames, 1983), and consequently damaging cellular lipids, proteins and DNA inducing lipid peroxides, protein carbonyls and DNA damage (Cerutti, 1985; Henson and Johnston, 1987; Wiesman and Halliwell, 1996). Environmental agents, which generate free radical are numerous and include alcohol, numerous food sources (Ames, 1983), infectious organisms (Freeman and Crapo, 1982), most physical and chemical agents including ionizing radiation (Gisone et al., 2006), dust particles (Fujimura, 2000), asbestos (Dopp et al., 2005), and are also provoked during exercise (Xiao and Li, 2006)

ROS have been implicated in the pathogenesis of most diseased conditions (Favier, 2006). ROS are virtually implicated in every stage of vascular lesion formation, angiotensin II-dependent hypertension (Kazama et al., 2004), hyperhomocysteinemia (Dayal et al., 2006), diabetes (Moore, 2006), metabolic syndrome, (Erdos et al., 2004) inflammation together with ischaemia and reperfusion (Weiss, 1986), subarachnoid haemorrhage (Kim et al., 2002). ROS are also implicated chronic kidney diseases (Shah, 2006), liver diseases (Kouroumalis and Notas, 2006) peripheral arterial disease (Loffredo et al., 2006), Alzheimer's disease (Onyango and Khan, 2006) and many others. Genetic variabilities in intensity of free radicals generation in response to external stressors and environmental stimuli in humans are largely unknown. However, the most striking example is chronic granulomatous diseases of childhood (CGD), which are a group of disorders in which, phagocytic cells are unable to produce superoxide (O^-_2) production from the respiratory burst system, due to defaults in the phagocyte NADPH oxidase, which is a complex system consisting of membrane and cytosolic components that must assemble at the membrane for proper activation. Lack in this system makes children succumb from infection and die at an early age (Nouni et al., 1998).

Nitric oxide (NO) has been identified as a widespread and multifunctional biological messenger molecule in the central nervous system (CNS), with

possible roles in neurotransmission, neurosecretion, synaptic plasticity, and tissue injury in many neurological disorders, including schizophrenia. Nitric oxide (NO) has been identified as a widespread and multifunctional biological messenger molecule produced in several types of mammalian cells including CNS, PMNs, macrophages and muscle cells. It participates in a broad range of important physiologic processes, including vasodilatation, neurotransmission, neurosecretion, synaptic plasticity, and host defence (Nathan and Xie, 1994). NO is generated from the amino acid L-arginine by three isoforms of the enzyme NO synthase; the constitutive (cNOS), the endothelial (eNOS) and the inducible (iNOS). The inducible form generates much larger amounts of NO (1,000 times fold than the other two isoforms) and its cellular production continues for many hours (Nathan, 1992). Inducible NOS has been detected in virtually every cell type, and the NO that it produces can perform both beneficial and detrimental actions, where, in physiological amounts, it is the key signal molecule in cell–cell interactions controlling vascular regulation (Clough, 1999) and neuronal communication (Yang and Hatton, 2002), NO can eliminate infiltrating microorganisms (James, 1995), reduce thrombosis, and improve blood supply to injured tissues (Gross and Wolin, 1995). NO can be detrimental, where excess production of NO can cause tissue damage and contribute to the development of a wide spectrum of diseases including septic shock, rheumatoid arthritis, cerebral ischaemia, multiple sclerosis, and diabetes (Nathan, 1992). On the contrary, NO deficiency may contribute to cardiovascular events and progression of kidney damage at end stage renal disease (Boger and Zoccali, 2003). Also loss of endothelial cell-derived nitric oxide (NO) in hypertension is a hallmark of arterial dysfunction as it is associated with decreased arterial vasodilator activity (Thakali et al., 2006). Concurrently, decreased NO levels are closely associated with preeclampsia-related endothelial dysfunction (Var et al., 2003).

Several studies suggest that the nitric oxide synthases gene polymorphism may confer increased susceptibility to several diseases. Increased NO generation has been reported to be caused by a mutation at the C150T iNOS. C150T iNOS polymorphism is associated with the risk of H pylori-related gastric cancer in a Japanese population. And is related to increasing the risk of gastric cancer in Asian countries with the highest rates of gastric cancer (Goto et al., 2006). This polymorphism is also associated with cigarette- and alcohol-induced gastric cancer in Chinese population (Shen et al., 2004). Decreased NO generation is caused by a mutation in eNOS gene promoter T-786C single nucleotide polymorphism. eNOS T-786C SNP has been shown to predict susceptibility to post-subarachnoid haemorrhage vasospasm (Khurana et al., 2004), and rheumatoid arthritis (Melchers et al., 2006). T-786C has been suggested to be an important risk factor in the development of

non-arteritic anterior ischaemic optic neuropathy (NAION) among Japanese subjects and is associated with a higher risk of multivessel coronary artery disease in Caucasians (Rossi et al., 2003). It is believed that high salt intake interacts with the T-786C mutation and leads to a significant increase in the risk of hypertension (Miyaki et al., 2005). Severity of carotid atherosclerosis is linked to the eNOS G/T polymorphism (Glu298Asp variant) (Spoto et al., 2005). The endothelial nitric oxide synthase (eNOS) gene is responsible for constitutive nitric oxide synthesis and arterial vasodilatation. 4a allele of the eNOS gene is related to elevated blood pressure levels particularly among type 2 diabetic patients with coronary heart disease (Zhang et al., 2006).

Agents known to induce the expression of iNOS mRNA are numerous and some of them include UV (Artiukhov et al., 2005), ionizing radiation (Chi et al., 2006), Helium neon laser (El Batanouny and Korraa, 2002), ozone (Fakhrzadeh et al., 2004), hypoxia (Lu et al., 2006), fly ash particles (Gursinsky et al., 2006) and asbestos (Sandrini et al., 2006). Morphin (Frenklakh et al., 2006) and dioxin (Cheng et al., 2003; Kuchiiwa, 2003) administration down-regulates NO production, while hydrogen sulphide can inhibit NO production in LPS-stimulated macrophages (Oh et al., 2006). Silymarin, a polyphenolic flavonoid antioxidant, inhibits NO production and iNOS gene expression (Kang et al., 2002) and 2-Chloroethyl ethyl sulphide (CEES) is a sulphur vesicating agent and an analogue of the chemical warfare agent 2,2′-dichlorodiethyl sulphide, or sulphur mustard gas (HD) decreases iNOS expression in murine macrophages (Qui et al., 2006)

BIOLOGICAL VARIABILITY IN NUCLEAR TRANSCRIPTION FACTORS ACTIVITY

Altering gene expression is the fundamental and effective way for a cell to respond to extracellular signals or environmental stresses in short- or long-term responses (D'Angio and Finkelstein, 2000). In the short term, transcription factors are involved in mediating responses to growth factors and a variety of other extracellular signals (Cosma, 2002). Regulation of the signaling responses is governed at the genetic level by transcription factors that bind to control regions of target genes and alter their expression (Alder et al., 1999). Transcription factors are endogenous DNA-binding proteins that enhance the transcription phase proteins by regulating gene expression of a variety of genes and are required for maximal transcription of many cytokines. They are effective in the initiation, stimulation or termination of the genetic transcription process. (Chu and Chang, 1988; Escoubet-Lozach et al., 2002) While in the cytoplasm, the transcription factor is incapable of promoting transcription. The activity of transcription factors is typically

regulated by phosphorylation-dependent events that can include the phosphorylation of the transcription factor itself; a signaling event occurs, leading to a change of the state of phosphorylation, followed by protein subunit translocation into the nucleus (Whitmarsh and Davis, 2000).

An example of these nuclear transcription factors is the Hypoxia-inducible factor 1 (HIF-1), which functions as a master regulator of oxygen homeostasis. HIF-1 consists of a constitutively expressed HIF-1β subunit and an oxygen-regulated HIF-1α subunit. Under hypoxic conditions, HIF-1α protein accumulates and translocates to the nucleus where it forms an active complex with HIF-1β, which activates transcription of >60 target genes important for the adaptation and survival under hypoxia (Semenza, 2003). HIF-1 target genes encode proteins that increase oxygen delivery, such as angiogenic factors (Tanimoto et al., 2003), as well as proteins that mediate adaptive responses to oxygen deprivation in ischaemic tissue, such as glucose transporters and glycolytic enzymes (Semenza, 2000). Genetic variations in HIF-1α genotype have been reported. HIF-1α may influence development of coronary artery collaterals in patients with significant coronary artery disease (Kelly et al., 2003), where the development of collateral circulation plays an important role in protecting tissues from ischaemic damage. Clinical observations have documented substantial differences in the extent of collateralization among patients with coronary artery disease, with some individuals demonstrating marked abundance and others showing nearly complete absence of these vessels (Resar et al., 2005). Mutation in two nucleotide sequence variants in exon 12 of the human *HIF1A* gene that affect the coding sequence of HIF-1α were lately reported to be present in patients with renal cell carcinoma (Clifford et al., 2001).

Hypoxia-inducible factor 1 (HIF-1) is affected by external stressors, where smoking damages the human placenta by altering the expression of HIFs, which play a key role in enhancing mediators of placental development (Genbacev et al., 2003). Carbon monoxide suppresses the activation of HIF-1 by hypoxia in a dose-dependent manner (Huang et al., 1999) by decreasing the binding of HIF-1 to its enhancer as exhibited by nuclear proteins isolated from CO-treated cells (Lui et al., 1998). HIF-1α is also overexpressed in the vast majority of patients with squamous cell cancer of the oropharynx and the degree of its expression has predictive and prognostic significance in individuals undergoing curative radiation therapy (Aebersod et al., 2001).

Another nuclear transcription factor is the nuclear transcription factor κB (NF-κB). It designates a group of critical transcription factors involved in a variety of immunologic and/or inflammatory processes and apoptosis in response to external stressors in many cell types. The predominant complex of NF-κB in most mammalian cells is p50/p65. NF-κB is required for maximal transcription of many cytokines, including tumour necrosis factor

(TNF-), interleukin-1 (IL-1), IL-2, IL-6, and IL-8, which are thought to be important in the generation of acute inflammatory responses (Siebenlist et al., 1994).

NF-κB activation was shown to be stimulated by alcohol consumption (Jaruga et al., 2004), bacterial endotoxin, chemical mitogens, viral proteins (Parsonnet, 1995), and certain chemical agents including ozone (Fakhrzadeh et al., 2004), arsenic and chromium (Ding et al., 2000; Dong, 2002) and asbestos (Faux and J. Howden, 1997). Excessive activation of NF-κB in leucocytes is stimulated by Short wavelength UV (Li and Karin, 1998; Wu et al., 2004) and ionising radiation in a dose-response pattern (Iarilin, 1999). There is an increasing body of evidence suggesting a role for NF-κB in carcinogenesis (Baldwin, 1996). For example, NF-κB is implicated in signaling tumour promoter-induced transformation and is activated by viral-transforming proteins (Dahr et al., 2002). The importance of NF-κB cannot be overstated, as failure in any of the mechanisms leading to NF-κB activation can have serious consequences for the cell. Impaired ability to signal and activate specific gene transcription through NF-κB has been directly linked to immunodeficiency (Uzel, 2005). Agents such as hydrogen sulphide can inhibit NO NF-κB activation in LPS-stimulated macrophages (Oh et al., 2006). Silymarin, a polyphenolic flavonoid antioxidant (Kang et al., 2002), and mustard gas analogue (Qui et al., 2006) individually inhibits NF-κB activation.

Concurrently, the constitutive activation of NF-κB has been linked with a wide variety of human diseases, including asthma, atherosclerosis, AIDS, rheumatoid arthritis, diabetes, osteoporosis, Alzheimer's disease, and cancer. Several agents are known to suppress NF-κB activation, including Th2 cytokines (IL-4, IL-13, and IL-10), interferons, endocrine hormones (LH, HCG, MSH and GH), phytochemicals, corticosteroids, and immunosuppressive agents. Because of the strong link of NF-κB with different stress signals, it has been called a "smoke-sensor" of the body (Ahn and Aggarwal, 2005). Polymorphism in the promoter region of the human NFKB1 gene was found to be associated with susceptibility to ulcerative colitis (Borm et al., 2005). Hippocampal pyramidal neurons in mice lacking the p50 subunit of NF-κB ($p50^{-/-}$) exhibit increased damage after exposures to excitotoxins (Yu et al., 1999; Kassed et al., 2002).

Antioxidant Enzymes, encoded by numerous genes in mammalian systems, have been shown to be responsive to oxidants, although a systematic mechanism for gene regulation by oxidative stress has not been elucidated. Oxidative stress has been shown to alter the expression of mammalian antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPx),ά;-glutamylcysteine synthetase, catalase, glutathione S-transferase and quinone reductase (Amstad and Cerutti, 1990). SOD catalyses the dismutation

of superoxide radicals into hydrogen peroxide that glutathione peroxidase and catalase break down into water (Halliwell, 1994). Induction of antioxidants by oxidative stress may both function in intracellular signalling and serve to protect cells from further oxidant injury. Accordingly, an imbalance in antioxidant mechanisms may influence cellular sensitivity to free-radical damage and alter susceptibility to disease (Ames, 1983).

Antioxidant enzymes especially the inducible SOD enzyme has been shown to be elevated in individuals at risk of exposure to low doses of various stresses. Superoxide dismutases (SODs) are the major antioxidant enzymes that inactivate superoxide and thereby control oxidative stress as well as redox signaling.

There are three types of mammalian SODs: manganese SOD (MnSOD) on the mitochondria, copper-zinc SOD on the cytosol and extracellular SOD in extracellular compartments (Zelko et al., 2002). Cigarette smokers (Kanehira et al., 2006), asbestos exposed workers (Kamal et al., 1992), radiotherapy exposed patients (Vucic et al., 2006), and athletes have higher levels of SOD enzymes compared to controls (Elosua et al., 2003). Asthmatic Chinese patients were shown to have elevated erythrocyte SOD activities in comparison with healthy controls (Mak et al., 2006). Also the antioxidant enzyme SOD in samples from patients with malignant tumours revealed up to 45-fold greater than that of controls (Yoshii et al., 1999; Soini et al., 2006).

MnSOD locus has been linked to the atherogenic lipoprotein phenotype, i.e. the excess of small dense LDL in humans (Allayee et al., 1998). Overexpression of MnSOD has been shown to protect transgenic mice against myocardial ischaemia (Cheng et al., 1998) and in rabbits to reverse vascular dysfunction in carotid arteries without atherosclerotic changes, but not in vessels with atherosclerotic plaques (Zanetti et al., 2001). Overexpression of MnSOD inhibits in vitro oxidation of LDL by endothelial cells (Fang et al., 1998) and ox-LDL is able to induce the expression of MnSOD in macrophages (Kinscherf et al., 1997). The apoE-deficient mice lacking MnSOD had more severe atherosclerosis compared to the apoE-deficient mice (Ballinger et al., 2002). In addition, the signal sequence polymorphism of the MnSOD gene has been associated with non-familial dilated cardiomyopathy in Japanese subjects (Hiroi et al., 1999), but it has not been investigated earlier in human atherosclerosis. It is suggested that MnSOD has a protective role for in retinal capillary cell death and, ultimately, in the pathogenesis of diabetes induced retinopathy (Kowluruet et al., 2006).

Extracellular SOD (ECSOD or SOD 3) is a major extracellular antioxidant enzyme. It distributed in the extracellular matrix of many tissues and especially blood vessels (Strålin et al., 1995). A fundamental property of ECSOD is its affinity, through its heparin-binding domain (HBD), for heparan sulphate

proteoglycans located on cell surfaces and in extracellular matrix (Sandström et al., 1992, 1993). It has been demonstrated that vascular effects of ECSOD require an intact HBD (Fattman et al., 2003). A common genetic variant with a substitution in the HBD (ECSOD(R213G) was reported recently to be associated with ischaemic heart disease. is a major extracellular antioxidant enzyme and it is suggested that human beings carrying ECSOD(R213G) are predisposed to vascular diseases (Chu et al., 2005)

Substitution of arginine-213 by glycine (R213G), which results from a C-to-G transversion at the first base of codon 213, is a common human gene variant in the HBD of ECSOD (Sandström et al., 1994). Plasma concentrations of ECSOD are increased greatly in the 2–5% of the population that carries $ECSOD_{R213G}$ (Adachi et al., 1996). This alteration in the HBD reduces affinity for heparin but does not affect the enzymatic activity of ECSOD. ECSOD affected individuals in Sweden, who did not have major phenotypic abnormalities, but there was a trend for increased triglycerides and body weight (Marklund et al., 1997). A recent large study in Denmark suggested a 2.3-fold increase in risk of ischaemic heart disease in heterozygotes carrying $ECSOD_{R213G}$, with a 9-fold increase after adjustment for plasma levels of ECSOD (Busse, 2001).

Glutathione peroxidase (GPX1), is an intracellular selenium-dependent enzyme that is ubiquitously expressed and detoxifies hydrogen and lipid peroxides plays a significant role in protecting cells from the oxidative stress induced by ROS. GPX1 levels are particularly responsive to fluctuations in selenium levels compared with other selenoproteins. Mice null for Gpx1 and GPx2 exhibit severe ileocolitis at a young age and develop microflora-associated cancers in the lower gastrointestinal tract (Chu et al., 2004).

GPX1 is polymorphic at codon 198, resulting in either a proline or a leucine at that position, and the frequency of the leu allele is strongly associated with an increase in the risk for lung (Ratnasinghe et al., 2000), and possibly breast cancer (Hu et al., 2004). The identity of the amino acid at codon 198 (proline or leucine) has functional consequences with regard to level of enzyme activity in response to increasing levels of selenium provided to cells in culture (Hu and Diamond, 2003). Loss of heterozygosity (LOH) occurs at the *GPX1* locus during the development of several cancer types, including those occurring in lung, breast, and head and neck (Moscow et al., 1994). In the case of head and neck cancers, *GPX1* allelic loss was shown to occur in histopathologically normal tissue adjacent to tumours, indicating that loss at this locus may be an early event in cancer evolution (Hu et al., 2004).

Meanwhile, GPX1 codon 198 polymorphism was associated with an increased risk of lung cancer and individuals carrying the Pro/Leu or Leu/Leu genotype of GPX1 were at a higher risk for lung cancer and were shown to have high urinary 8-OH-dG concentrations compared to the individuals

with the GPX1 Pro/Pro genotype. On the other hand, the polymorphism of the hOGG1 gene did not affect the lung cancer risk and the oxidative DNA damage (Lee et al., 2006)

Catalase enzyme is an endogenous antioxidant enzyme that neutralizes ROS by converting H_2O_2 into H_2O and O_2. A −262C →T polymorphism in the promoter region of the gene (CAT) is associated with risk of several conditions related to oxidative stress. It is plausible that the endogenous variability associated with this polymorphism plays a role in the host response to oxidative stress and progression to breast cancer (Ambrosone, 2000). Asthma patients due to polymorphism in the C allele of catalase gene at C-262T had elevated erythrocyte CAT activities in comparison with healthy controls in Hong Kong (Mak et al., 2006).

BIOLOGICAL VARIABILITY IN DNA REPAIR CAPACITY

DNA repair processes restore the normal nucleotide sequence and DNA structure after damage. It assists in maintaining genomic integrity by removing inappropriate bases and other possible deleterious lesions from DNA. Overlap among these pathways exists in terms of the types of damage removed by each. The complex series of DNA repair pathways employ many different proteins. Numerous DNA repair mechanisms have been identified: (i) site-specific repair (ii) nucleotide excision repair (NER), (iii) base excision repair, (iv) mismatch repair (MMR), (v) direct reversal of the damage, in which no incision is made in the backbone of the DNA (Bohr et al., 1987). An increased incidence of neoplasia is correlated with a defect in the repair or replication of damaged DNA in some human genetic diseases. Examples of such hereditary disorders include xeroderma pigmentosum, ataxia telangiectasia, Fanconi's anaemia, and Bloom's syndrome (Fuss and Cooper, 2006). Several types of cancer have been linked with defects in all types of DNA repair pathways. For example, hereditary nonpolyposis colon cancer results from defects in MMR genes, and hereditary breast cancer is caused by mutations affecting the breast cancer associated proteins BRCA1 or BRCA2 that play a role in DSB repair by homologous recombination (Fuss and Cooper, 2006). Patients with multiple sclerosis were shown to exhibit reduced DNA excision reparation capacity in their peripheral blood lymphocytes which correlated with the disease severity but not with its duration (Moskaleva et al., 1988).

The biological consequences of unrepaired or misrepaired DNA damage depend on the precise locations of the lesions. DNA lesions at specific sites in the mammalian genome can lead to mutation, recombination, gene amplification, translocation, and other chromosomal abnormalities. These changes in turn may result in malignant transformation, faulty differentiation patterns, or cell death. Thus, it has become clear that damage to DNA at particular

loci can cause activation of the protooncogenes and inactivation of tumour suppressor genes that may be implicated in subsequent tumourigenesis and age-related diseases (1). There is increasing evidence that human atherosclerosis is associated with damage to the suppressor gene p53 of both circulating cells, and cells of the vessel wall. DNA damage produces a variety of responses, including cell senescence, apoptosis and DNA repair. Decreased endogenous levels of p53 promotes plaque formation in vascular muscle smooth cells and stromal cells by promoting apoptosis, while inhibiting apoptosis in macrophages, leading to atherosclerosis development (Mercer et al., 2005). Similarly, in rheumatoid arthritis, oxidative damage caused by inflammation appears to cause *p53* mutations in synovium Most of the p53 mutations in RA are characterized by transition base changes (Inazuka et al., 2000). Furthermore, certain p53 mutations in RA are dominant negative and can suppress endogenous wild-type p53 function (Han et al., 1999). Inactivation of p53 protein can recapitulate many of the phenotypic changes observed in RA, such as increased proliferation and invasion of synovial cells (Aupperle et al., 1998; Pap et al., 2001). Elevated levels of DNA alkylation damage have been detected in schistosome-infected bladders and are accompanied by an inefficient capacity of DNA repair mechanisms. Consequently, high frequency of G → A transition mutations were observed in the H-ras gene and at the CpG sequences of the p53 tumour suppressor gene (Badawi, 1996). It is suggested that the excess of transitions at CpG dinucleotides in squamous cell carcinoma induced by Bilharzial infections results from nitric oxide (NO) produced by the inflammatory response provoked by schistosomal eggs. NO could produce such mutations directly, by deamination of 5-methylcytosine, and indirectly, following conversion to nitrate, bacterial reduction to nitrite and endogenous formation of urinary N-nitroso compounds. These produce O6-alkylguanines in DNA, leading to very high rates of G:C→A:T transitions, a process possibly augmented by inefficient repair of alkylated bases at CpG dinucleotides (Warren et al., 1995). DNA repair capacity decreases by ageing (Cabelof et al., 2006) giving clue to the increased incidence of ageing associated diseases.

INDUCTION OF APOPTOSIS

Apoptosis or programmed cell death is a gene-regulated process in which a coordinated series of morphological changes such as nucleus and chromatin condensation, cell membrane blebbing and fragmentation of the cell into membrane-bound apoptotic bodies occurs, resulting in cell death (Barazzone and White, 2000). It is accepted that morphological changes observed during programmed cell death are the consequence of an activation of caspases cascade (Green, 1998). At least two main signaling pathways have been

postulated to participate in this process. The first one involves membrane receptors called death receptors (i.e. TNF receptor-1 and Fas/Apo-1) (Mak and Yeh, 1999; Hengartner, 2000), and the second one relies on the cell's ability to sense changes in the ratio between the protein levels of the members of the Bcl-2 family. Bcl-2 prevents apoptosis induced by a wide range of stimuli, suggesting that different pathways of transduction signals converge at this point (Adams and Cory, 1998; Zornig et al., 2001).

Membrane receptors include FAS (also known as TNFSF6, CD95, or APO-1), which is a cell surface receptor that plays a central role in apoptotic signaling in many cell types (Nagata and Goldstein, 1995). This receptor interacts with its natural ligand FASL (also known as CD95L), a member of the tumour necrosis factor superfamily, to initiate the death signal cascade, which results in apoptotic cell death (Reichmann, 2002). An immuno-privileged status for tumours is established via the FAS-mediated apoptosis of tumour-specific lymphocytes (Nagata and Goldstein, 1995). Decreased expression of FAS and/or increased expression of FASL favors malignant transformation and progression [for a review, see (Muschen et al., 2000). In addition, functional germline and somatic mutations in the FAS gene and perhaps also in the FASL gene that impair apoptotic signal transduction are associated with a high risk of cancer. Thus, the FAS/FASL system appears to have a role in the development and progression of cancer (Lee et al., 1999).

Mitochondria play a key role in the apoptotic pathway through the release of several factors from the intermembrane space to the cytoplasm, such as cytochrome C (Liu et al., 1996). It has been suggested that this pathway could be regulated by the relative levels and subcellular distribution of Bcl-2 family proteins. The antiapoptotic members (i.e. Bcl-2 or Bcl-X_L) are mostly associated to the outer membrane of mitochondria and inhibit cytochrome C release. On the other hand, the proapoptotic molecules such as Bax, Bad, or Bid are cytosolic proteins; they translocate to the mitochondria and trigger cytochrome C release on apoptosis induction Several authors have identified a variety of proteins related with Bcl-2, such as Bax, Bak, Bid, and the different Bcl-X isoforms, which can either promote or prevent apoptosis (Cory, 1995).

Apoptosis plays an important role in sculpting the developing organism and eliminating unwanted or potentially dangerous cells throughout life. Abnormal regulation of apoptosis is associated with a variety of diseases. Cells that should die but do not can cause cancer and autoimmune diseases, whereas cells that should not die but do can cause stroke and neurodegenerative disorders (Thompson, 1995). The adaptive increase in apoptosis that accompanies the oncogene-activated dysregulation in proliferation selectively eliminates potentially preneoplastic cells in hyperplastic foci. Acquired resistance to apoptosis appears to be a pivotal event in the transition to malignancy (Schulte-Hermann

et al., 1995). The homeostatic balance between cell proliferation and apoptosis in the maintenance of constant cell numbers may provide a hormetic effect by minimizing the consequences of proliferation-related mutagenesis during tumour promotion (McDonnell, 1993; Meikrantz and Schlegel, 1995).

In conclusion, it has been long established that when organisms or cells are exposed to low levels of specific harmful physical or chemical agents, a beneficial physiologic effect is observed. Concurrently; exposure to sublethal challenges of stress may rejuvenate the cell by repairing damage before the challenge and may provide transient protection against further damage from subsequent sublethal or lethal challenges with a different otherwise harmful physical or chemical stressor. Due to the wide variation in individual responses to exogenous agents is believed to result from the great diversity in responsiveness to risk factors in the environment. Detectable gene mutations and alterations in signal transduction pathways together with modified post-translational proteins offer valuable molecular biomarkers for occupational and environmental human biomonitoring applied for the identification of potentially hazardous exposures before adverse health effects appear and allow the establishment of exposure limits in order to minimize the likelihood of significant health risks. Concurrently, most of these elicited gene expressions are also expressed in tissue transformation and progression of tumours and are similar to the hallmarks used for cancer prognosis. Some of these proteins represent protective mechanisms against different environmental stresses, while others amplify adaptation to environmental conditions. The resultant balance between protective proteins and adaptive proteins seem to determine an individual likelihood to develop diseases.

References

Adachi, T., Yamada, H., Yamada, Y., Morihara, N., Yamazaki. N., Murakami, T., Futenma, A., Kato, K., Hirano, K., 1996, Substitution of glycine for arginine-2.13 in extracellular-superoxide dismutase impairs affinity for heparin and endothelial cell surface. *Biochem. J*. 313: 235–239.

Adams, J. and Cory, S., 1998, The Bcl-2 protein family: arbiters of cell survival. *Science* 281: 1322–1326.

Aebersod, D., Burri, P., Beer, K., Laissue J., Djonov, V., Greiner, R., and Semenza G. L., 2001, Expression of hypoxia-inducible factor-1alpha: a novel predictive and prognostic parameter in the radiotherapy of oropharyngeal cancer. *Cancer Res*. 61(7): 2911–2916.

Ahn, K., and Aggarwal, B., 2005, Transcription Factor NF-{kappa}B: A Sensor for Smoke and Stress Signals. *Ann. NY Acad. Sci*. 1056: 218–233.

Alder, V., Yin, Z., Tew, K. D., and Ronai, Z., 1999, Role of redox potential and reactive oxygen species in stress signaling. *Oncogene* 18: 6104–6111.

Allayee, H., Aouizerat, B., Cantor, R., Dallinge-Thie, G., Krauss, R., Lanning, C., Rotter, J., Lusis, A., and de Briun, T., 1998, Families with familial combined hyperlipidemia and families enriched for coronary artery disease share genetic determinants for the atherogenic lipoprotein phenotype. *Am. J. Hum. Genet*. 63(2): 577–585.

Ambrosone, C., 2000, Oxidants and antioxidants in breast cancer. *Antioxid. Redox Signal* 2: 903–917.

Ames, B., 1983, Dietary carcinogens and anticarcinogens, *Science* 121: 1250–1264.
Amstad, P., and Cerutti, P., 1990, Genetic modulation of the cellular antioxidant defense capacity, *Environ. Health Perspect*. 88: 77–82.
Artiukhov, V., Gusinskaia, V., and Mikhileva, E., 2005, Level of nitric oxide and tumor necrosis factor-alpha production by human blood neutrophils under UV-irradiation. *Radiat. Biol. Radioecol*. 45(5): 576–580.
Attene-Ramos, M., Kitiphongspattana, K., Ishii-Schrade, K., and Gaskins, H., 2005, Temporal changes of multiple redox couples from proliferation to growth arrest in IEC-6 intestinal epithelial cells, *Am. J. Physiol. Cell Physiol*. 289(5): C1220–C1228.
Au, W., Wilkinson, G., Tyring, S., Legator, M., El Zein, R., Hallberg, L., and Heo, M., 1996, Monitoring populations for DNA repair deficiency and for cancer susceptibility. *Environ. Health Perspect*. 104(Suppl 3): 579–584.
Aupperle, K., Boyle, D., Hendrix, M., Seftor, E., Zvaifler, N., Barbosa, M., and Firestein, G., 1998, Regulation of synoviocyte proliferation, apoptosis, and invasion by the p53 tumor suppressor gene. *Am. J. Pathol*. 152: 1091–1098.
Badawi, A., 1996, Molecular and genetic events in schistosomiasis-associated human bladder cancer: role of oncogenes and tumor suppressor genes. *Cancer Lett*. 105(2): 123–138.
Baldwin A., 1996, The NF-κB and IκB Proteins: New Discoveries and Insights. *Ann. Rev. Immunol*. 14: 649–681.
Ballinger, S., Patterson, C., Knight-Lozano, C., Burow, D. et al., 2002, Mitochondrial integrity and function in atherogenesis. *Circulation* 106: 544–549.
Barazzone, C. and White, C., 2000, Mechanisms of cell injury and death in hyperoxia. Role of cytokines and Bcl-2 family proteins. *Am. J. Resp. Cell Mol. Biol*. 22: 517–519.
Brennan, P., 2002**,** Gene–environment interaction and aetiology of cancer: what does it mean and how can we measure it? *Carcinogenesis* 23(3): 381–387.
Boger, R. and Zoccali, G., 2003, ADMA: a novel risk factor that explains excess cardiovascular event rate in patients with end-stage renal disease. *Atheroscler. Suppl*. 4(4): 23–28.
Bohr, V., Phillips, D., and Hanawalt, P., 1987, Heterogeneous DNA damage and repair in the mammalian genome. *Cancer Res*. 47: 6426–6436.
Borm, M., van Bodegraven, A., Mulder, C., Kraal, G., Bouma, G., 2005, A NFKB1 promoter polymorphism is involved in susceptibility to ulcerative colitis. *Int. J. Immunogenet*. 32(6): 401.
Bove, P. and van der Vilet, A., 2006, Nitric oxide and reactive nitrogen species in airway epithelial signaling and inflammation. *Free Rad. Biol. Med*. 41(4): 515–527.
Busse, W. and Lemanske, R., 2001, Asthma. *N. Engl. J. Med*. 344: 350–362.
Cabelof. D., Raffoul, J., Ge, Y., Van Remmen, H., Matherly, L., and Hedari, A., 2006, Age-related loss of the DNA repair response following exposure to oxidative stress. *J. Gerontol. A Biol. Sci. Med. Sci*. 61(5): 427–434.
Cemerski, S., Cantagrl, A., Van Meerwijki, J., and Romagnoli, P., 2002. Immediate and delayed VEGF-mediated NO synthesis in endothelial cells: role of PI3K, PKC and PLC pathways. *Br. J. Pharmacol*. 137(7): 1021–1030.
Cerutti, P., 1985, Prooxidant states and tumor promotion. *Science* 227: 375–381.
Chen, L., Knutsen, S., Shavlik, D., Beeson W., Petersen, F., Ghamsary, M., and David, A., 2005, The association between fatal coronary heart disease and ambient particulate air pollution: are females at greater risk? *Environ. Health. Perspect*. 113 (12): 1723–1729.
Cheng, S., Kuchiiwa, S., Ren, X., Gao, H., Kuchiiwa, T., and Nakagawa, S., 2003, Dioxin exposure down-regulates nitric oxide synthase and NADPH-diaphorase activities in the hypothalamus of Long-Evans rat. *Neurosci. Lett*. 345(1): 5–8.
Cheng, S., Chen, Z., Siu, B., Ho, Y., Vincent R et al., 1998, Overexpression of MnSOD protects against myocardial ischemia/reperfusion injury in transgenic mice. *J. Mol. Cell. Cardiol*. 30: 2281–2289.
Cory, S., 1995, Regulation of lymphocyte survival by the bcl-2 gene family. *Annu. Rev. Immunol*. 13: 513–543.
Chi, C., Ozawa, T., and Anazi, T., 2006, In vivo nitric oxide production and iNOS expression in X-ray irradiated mouse skin. *Biol. Pharm. Bull*. 29(2): 348–353.

Chu, G. and Chang, E., 1988, Xeroderma Pigmentosum Group E Cells Lack a Nuclear Factor that Binds to Damaged DNA, *Science* 242: 564–567.

Chu, F., Esworthy, R., Chu, P., Longmate, J., Huycke, M., Wilczynski, S., and Doroshow, J., 2004, Bacteria-induced intestinal cancer in mice with disrupted Gpx1 and Gpx2 genes. *Cancer Res*. 64: 962–968.

Chu, Y., Alwahdani, A., Iida, S., Lund, D., Faraci, F., and Heistad, D., 2005, Vascular effects of the human extracellular superoxide dismutase R213G variant. *Circulation* 112(7): 1047–1053.

Clifford, S., Astuti, D., Hooper, L., Maxwell, P., Ratcliffe, P., and Maher E., 2001, The pVHL-associated SCF ubiquitin ligase complex: molecular genetic analysis of elongin Band C, Rbx1, and HIF-1α in renal cell carcinoma. *Oncogene* 20: 5067–5074.

Clough, G., 1999, Role of nitric oxide in the regulation of microvascular perfusion in human skin in vivo. *J. Physiol*. 516: 549–557.

Cosma, M., 2002, Ordered recruitment: gene-specific mechanism of transcription activation. *Mol. Cell* 10(2): 227–236.

D'Angio, C., and Finkelstein, J., 2000, Oxygen regulation of gene expression: a study in opposites. *Mol. Genet. Metab*. 71: 371–380.

Dahr, A., Young, M., and Colbum, N., 2002, The role of AP-1, NF-kappaB and ROS/NOS in skin carcinogenesis: the JB6 model is predictive. *Mol. Cell Biochem*. 234–235(1–2): 185–193.

Dayal, S., Wilson, K., Leo, L., Aming, E., Bottiglieri, T., and Lentz, S., 2006, Enhanced susceptibility to arterial thrombosis in a murine model of hyperhomocysteinemia. *Blood* 108(7): 2237–2243.

Ding, M., Shi, X., Castranova, V., and Vallyathan, V., 2000, Predisposing factors in occupational lung cancer: inorganic minerals and chromium. *J. Environ. Pathol. Toxicol. Oncol*. 19(1–2): 129–138.

Dong, Z., 2002, The molecular mechanisms of arsenic-induced cell transformation and apoptosis. *Environ. Health Perspect*. 110(Suppl 5): 757–759.

Dooly, M. and Hogan, S., 2003, Environmental epidemiology and risk factors for autoimmune disease. *Curr. Opin. Rheumatol*. 15(2): 99–103.

Dopp, E., Yadav, S., Ansari, F., Bhattacharya, K., von Recklinghausen, U., Rauen, U., Rodelsperger, K., Shokouhi, B., Geh, S., and Rahman Q., 2005, ROS-mediated genotoxicity of asbestos-cement in mammalian lung cells in vitro. *Part. Fibre Toxicol*. 6: 2–9.

Eggleston, P., Buckley, T., Breysse, P., Wills-Karp, M., Kleeberger, S., and Jaakkola, J., 1999, The environment and asthma in U.S. inner cities. *Environ. Health Perspect*. 107(Suppl 3): 439–450.

Erdos, B., Snipes, J., Miller, A., and Busija, D., 2004, Cerebrovascular dysfunction in Zucker obese rats is mediated by oxidative stress and protein kinase C. *Diabetes* 53: 1352–1359.

El Batanouny, M. and Korraa, S., 2002, Effects of low intensity laser on the activity and expression of nitric oxide synthase in human polymorphonuclear leucocytes in vitro, *Arab J. Lab. Med*. 28(3): 289–297.

Elena, S. and de Visser, J., 2003, Environmental stress and the effects of mutation. *J. Biol*. 2(2): 12–17.

Elosua, R., Molina, L., Fito, M., Arquer, A., Sanchez-Quesada, J., Covas, M., Ordonez-Llanos, J., and Marrugat, J., 2003, Response of oxidative stress biomarkers to a 16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. *Atherosclerosis* 167(2): 327–334.

Escoubet-Lozach, L., Glass, C. K., and Wasserman, S. I, 2002, The role of transcription factors in allergic inflammation. *Allergy Clin. Immunol*. 110(4): 553–564.

Fakhrzadeh, L., Laskin, J., and Laskin, D., 2004, Ozone-induced production of nitric oxide and TNF-alpha and tissue injury are dependent on NF-kappaB p50. *Am. J. Physiol. Lung Cell Mol. Physiol*. 87(2): L279–L285.

Fang, X., Weintraub, N., Rios, C., Chappell D., et al., 1998, Overexpression of human superoxide dismutase inhibits oxidation of low-density lipoprotein by endothelial cells. *Circ. Res*. 82: 1289–1297.

Fattman, C., Schaefer, L., and Oury, T., 2003, Extracelluar superoxide dismutase in biology and medicine. *Free Radic. Biol. Med*. 35: 236–256.

Faux, S. and Howden, J., 1997, Possible Role of Lipid Peroxidation in the Induction of NF-κB and AP-1 in RFL-6 Cells by Crocidolite Asbestos: Evidence following Protection by Vitamin E. *Environ. Health Perspect*. 105(Suppl 5): 1127–1130.

Favier, A., 2006, Oxidative stress in human diseases. *Ann. Pharm. Fr*. 64(6): 390–396.

Fialkow, L., Chan, C., Rotin, D., Grinstein, S., and Downey, G., 1994, Activation of the mitogen-activated protein kinase signaling pathway in neutrophils. Role of oxidants. *J. Biol. Chem*. 269(49): 31234–31242.

Freeman, B., and Crapo, J., 1982, Biology of disease: free radicals and tissue injury. *Lab. Invest*. 47: 412–426.

Frenklakh, L., Bhat, R., Bhaskaran, M., Sharma, S., Sharma, M., Dinda, A., and Singhal, P., 2006, Morphine-induced degradation of the host defense barrier role of intestinal mucosal injury. *Dig. Dis. Sci*. 51(2): 318–325.

Fujimura, N., 2000, Pathology and pathophysiology of pneumoconiosis. *Curr. Opin. Pulm. Med*. 6: 140–144.

Fuss, J. and Cooper, P., 2006, DNA repair: dynamic defenders against cancer and aging. *PLoS. Biol*. 4(6): e203.

Genbacev, O., McMaster, M., Zdravkovic, T., and Fischer, S., 2003, Disruption of oxygen-regulated responses underlies pathological changes in the placentas of women who smoke or who are passively exposed to smoke during pregnancy. *Reprod. Toxicol*. 17(5): 509–518.

Gelinas, D., Bernatchez, P., Rollin, S., Bazan, N., and Sirois, M., 2002, Reactive oxygen species differentially affect T cell receptor-signaling pathways. *J. Biol. Chem*. 277(22): 19585–19593.

Gisone, P., Robello, E., Sanjurjo, J., Dubner, D., Perez Mdel R., Michelin, S. and Puntarulo, S., 2006, Reactive species and apoptosis of neural precursor cells after gamma-irradiation. *Neurotoxicology* 27(2): 253–259.

Goto, Y., Ando, T., Naito, M., Goto, H., and Hamajima N., 2006, Inducible nitric oxide synthase polymorphism is associated with the increased risk of differentiated gastric cancer in a Japanese population. *World J. Gastroenterol*. 12(39): 6361–6365.

Green, D., 1998, Apoptotic pathways: the roads to ruin. *Cell* 94: 695–698.

Greenblatt, M., Bennett, W., Hollstein, M., and Harris, C., 1994, Mutations in the *p53* tumor suppressor gene: clues to cancer etiology and molecular Pathogenesis. *Cancer Res*. 54(18): 4855–4878.

Gross, S. and Wolin, M., 1995, Nitric oxide: pathophysiological mechanisms. *Ann. Rev. Physiol*. 57: 737–769.

Gursinsky, T., Ruhs, S., Friess, U., Diabate, S., Krug, H., Silber, R., and Simm, A., 2006, Air pollution-associated fly ash particles induce fibrotic mechanisms in primary fibroblasts. *Biol. Chem*. 387(10–11): 1411–1420.

Guzik, T., Korbut, R., and Adamek-Guzik, T., 2003, Nitric oxide and superoxide in inflammation and immune regulation. *J. Physiol. Pharmacol*. 54(4): 469–487.

Halliwell, B., 1994, Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *Lancet* 344: 721–724.

Han, Z., Boyle, D. L., Shi, Y., Green, D., and Firestein, G., 1999, Dominant-negative p53 mutations in rheumatoid arthritis. *Arthritis Rheum*. 42: 1088–1092.

Henson, P. and Johnston, R., 1987, Tissue injury in inflammation, oxidants, proteinases and cationic proteins. *J. Clin. Invest*. 79: 669–674.

Hengartner, M., 2000, The biochemistry of apoptosis. *Nature* 407: 770–776.

Hiroi S., Harada, H., Nishi, H., Satoh, M., Nagai, R., and Kimura, A., 1999, Polymorphisms in the SOD2 and HLA-DRB1 genes are associated with nonfamilial idiopathic dilated cardiomyopathy in Japanese. *Biochem. Biophys. Res. Commun*. 261: 332–339.

Hsu, Y., Chen, J., Chang, C., Chen, C., Liu, J., Chen, T., Jeng, C., Chao, H., and Chen, T., 2004, Role of reactive oxygen species-sensitive extracellular signal-regulated kinase pathway in angiotensin II-induced endothelin-1 gene expression in vascular endothelial cells. *J. Vasc. Res*. 41(1): 64–74.

Hu, Y. and Diamond, A., 2003, Role of glutathione peroxidase 1 in breast cancer: loss of heterozygosity and allelic differences in the response to selenium. *Cancer Res*. 63: 3347–3351.

Hu, Y., Dolan, M., Bae, R., Yee, H., Roy, M., Glickman, R., Kiremidjian-Schumacher, L., and Diamond, A., 2004, Allelic Loss at the GPx-1 Locus in Cancer of the Head and Neck. *Biol. Trace Elem. Res*. 101: 97–106.

Huang, L., Willmore, W., Gu, J. Goldberg, M., and Bunn, H., 1999, Inhibition of hypoxia-inducible factor 1 activation by carbon monoxide and nitric oxide, Implications for oxygen sensing and signaling. *J. Biol. Chem*. 274(13): 9038–9044.

Iarilin, A., 1999, Radiation and immunity, interference of ionizing radiation with key immune processes. *Radiat. Biol. Radioecol*. 39(1): 181–189.

Inazuka, M., Tahira, T., Horiuchi, T., Harashima, S., Sawabe, T., Kondo, M., Miyahara, H., and Hayashi, K., 2000, Analysis of p53 tumour suppressor gene somatic mutations in rheumatoid arthritis synovium. *Rheumatology* 39: 262–266.

James, S., 1995, Role of nitric oxide in parasitic iInfection. *Microbiol. Rev*. 59(4): 533–547.

Jaruga, B., Hong, F., Kim, W., Sun, R., Fan, S., and Gao, B., 2004, Chronic alcohol consumption accelerates liver injury in T cell-mediated hepatitis: alcohol disregulation of NF-{kappa}B and STAT3 signaling pathways. *Am. J. Physiol. Gastrointest. Liver Physiol*. 87(2): G471–G47.

Kamal, A., Al Khafif, M., Massoud, A., and Korraa, S., 1992, Plasma lipid peroxide and blood superoxide dismutase among asbestos exposed workers. *Am. J. Indust. Med*. 21(31): 341–352.

Kandacova, N. and Zagrebel'naia, G.V., 2004, The influence of peroxide Radicals & nitric oxide on DNA synthesis in tumour cells. *Biomed. Khim*. 50: 566–575.

Kanehira, T., Shibata, K., Kashiwazaki, H., Inoue, N., and Morita, M., 2006, Comparison of antioxidant enzymes in saliva of elderly smokers and non-smokers. *Gerodontology*. 23(1): 38–42.

Kang, J., Jeon, Y., Kim, H., Hans, S., Han, S., and Yang, K., 2002, Inhibition of inducible nitric-oxide synthase expression by silymarin in lipopolysaccharide-stimulated macrophages. *J. Pharmacol. Exp. Ther*. 302(1): 138–144.

Kassed, C., Willing, A., Garbuzova-Davis, A., Sanberg, P., Pennypacker, K., 2002, Lack of NF-κB p50 exacerbates degeneration of hippocampal neurons after chemical exposure and impairs learning. *Exp. Neurol*. 176: 277–288.

Kazama, K., Anrather, J., Zhou, P., Girouard, H., Frys, K., Milner, T., and Iadecola, C., 2004, Angiotensin II impairs neurovascular coupling in neocortex through NADPH oxidase-derived radicals. *Circ. Res*. 95(10): 1019–1026.

Kelly, B., Hackett, S., Hirota, K., Oshima, Y., Cai, Z., Berg-Dioxin, S., Rowan, A., Yan, Z., Campochiaro, P., and Semensa, G., 2003, Cell type-specific regulation of angiogenic growth factor gene expression and induction of angiogenesis in nonischemic tissue by a constitutively active form of hypoxia-inducible factor 1. *Circ. Res*. 93: 1074–1081.

Khurana, V., Sohni, Y., Mangrum, W., McClelland, R., O'Kane, D., Meyer, D. and Meisser, I., 2004, Endothelial nitric oxide synthase gene polymorphisms predict susceptibility to aneurysmal subarachnoid hemorrhage and cerebral vasospasms. *J. Cereb. Blood Flow. Metab*. 24(3): 291–297.

Kim, D., Suh, Y., Lee, M., Kim, K., Lee J., Lee, H., Hong, K., and Kim, C., 2002, Vascular NAD(P)H oxidase triggers delayed cerebral vasospasm after subarachnoid hemorrhage in rats. *Stroke* 33: 2687–2691.

Kinscherf, R., Deigner, H., Usinger, C., Pill, J., Wagner, M., Kamencic, H., Hou, D., Chen, M., Schmiedt, W., Schrader, M., Kovacs, G., Kato, K., and Metz, J., 1997, Induction of mitochondrial manganese superoxide dismutase in macrophages by oxidized LDL: its relevance in atherosclerosis of humans and heritable hyperlipidemic rabbits. *FASEB J*. 11: 1317–1328.

Kouroumalis, E. and Notas, G., 2006, Pathogenesis of primary biliary cirrhosis: a unifying model. *World J. Gastroenterol*. 12(15): 2320–2327.

Kowluruet, R., Atasi, I., and Ho, Y., 2006, Role of mitochondrial superoxide dismutase in the development of diabetic retinopathy. *Invest. Ophthalmol. Vis. Sci*. 47(4): 1594–1599.

Kuchiiwa, S., Ren, X., Gao, H., Kuchiiwa, T., and Nakagawa, S., 2003, Dioxin exposure down-regulates nitric oxide synthase and NADPH-diaphorase activities in the hypothalamus of Long-Evans rat. *Neurosci. Lett*. 345(1): 5–8.

Lagorio, S., Forastiere, F., Pistelli, R., Iavarone, I., Michelozz, P., Fano, V., Marconi, A., Ziemacki, G., and Ostro, B., 2006, Air pollution and lung function among susceptible adult subjects: a panel study. *Environ. Health*. 5: 11–16.

Landrigan, P., Sonawane, B., Butler, R., Trasande, T., Richard, Callan, R., and Droller, D., 2005, Early environmental origins of neurodegenerative disease in later life. *Environ. Health Perspect*. 113(9): 1230–1233.

Lee, C., Lee, K., Choe, K., Hong, Y., Noh, S., Eom, S., Ko, Y., Zhang, y., Yim, D., Kang, J., Kim, H., and Kim Y., 2006, Effects of oxidative DNA damage and genetic polymorphism of the glutathione peroxidase 1 (GPX1) and 8-oxoguanine glycosylase 1 (hOGG1) on lung cancer. *J. Prev. Med. Pub. Health* 39(2): 130–134.

Lee, D., Lee, I., Song, K., Steffes, M., Toscano, W., Baker, B., and Jascobs, D., 2006, A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care* 29(7): 1638–1644.

Lee, S. H., Shin, M. S., Park, W. S., Kim, S. Y., Kim, S. H., Han, J. Y., et al., 1999, Alterations of Fas (Apo-1/CD95) gene in non-small cell lung cancer. *Oncogene* 18: 3754–3760.

Li, N. and Karin, M., 1998, Ionizing radiation and short wavelength UV activate NF-κB through two distinct mechanisms. *Cell Biol*. 95(22): 13012–13017.

Liu, X., Kim, C., Yang, J., Jemmerson, R., and Wang, X., 1996, Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. *Cell* 86: 147–157.

Loffredo, L., Pignatelli, P., Cangemi, R., Andreozzi, P., Panico, M., Meloni, V., and Violi, F., 2006, Imbalance between nitric oxide generation and oxidative stress in patients with peripheral arterial disease: effect of an antioxidant treatment. *J. Vasc. Surg*. 44(3): 525–530.

Lu, D., Liou, H., Tang, C., and Fu, W., 2006, Hypoxia-induced iNOS expression in microglia is regulated by the PI3-kinase/Akt/mTOR signaling pathway and activation of hypoxia inducible factor-1alpha. *Biochem. Pharmacol*. 72(8): 992–1000.

Lui, Y., Christou, H., Morita, T., Laughner, E., Semenza, G., and Kourembanas, S., 1998, Carbon monoxide and nitric oxide suppress the hypoxic induction of vascular endothelial growth factor gene via the 5 enhancer. *J. Biol. Chem*. 273(24): 15257–15262.

Mak, T. and Yeh, W., 1999, Genetic analysis of apoptotic and survival signals. *Cold Spring Harb. Symp. Quant. Biol*. 64: 335–342.

Mak, J., Leung, Ho, S., Ko, F., Cheung, A., Ip, M., and Chan-Yeung, M., 2006, Polymorphisms in manganese superoxide dismutase and catalase genes: functional study in Hong Kong Chinese asthma patients. *Clin. Exp. Allergy* 36(4): 440–447.

Malkin, D., 1995, Age-specific oncogenesis: the genetics of cancer susceptibility. *Environ. Health Perspect*. 103(Suppl 5): 45–48.

Marklund S., Nilsson, P., Israelsson, K, Schampi, I., Peltonen. M., Asplund. K., 1997, Two variants of extracellular-superoxide dismutase: relationship to cardiovascular risk factors in an unselected middle-aged population. *J. Intern. Med*. 242: 5–14.

McDonnell, T., 1993, Cell division versus cell death: a functional model of multistep neoplasia. *Mol. Carcinog*. 8: 209–213.

Meikrantz, W., and Schlegel, R., 1995, Apoptosis and the Cell Cycle. *J. Cell Biochem*. 58: 160–174.

Melchers, I., Blaschke, S., Hecker, M., and Cattaruzza, M., 2006, The -786C/T single-nucleotide polymorphism in the promoter of the gene for endothelial nitric oxide synthase: insensitivity to physiologic stimuli as a risk factor for rheumatoid arthritis. *Arthritis. Rheum*. 54(10): 3144–3151.

Mercer, I., Blashke, S., Hecker, M., and Cattaruzza, M., 2005, Endogenous p53 protects vascular smooth muscle cells from apoptosis and reduces atherosclerosis in ApoE knock-out mice. *Circ. Res*. 96(6): 667–674.

Miyaki, K., Tohyana, S., Murata, M., Kikuchi, H., Takei, I., Watanabe, K., and Omae K., 2005, Salt intake affects the relation between hypertension and the T-786C polymorphism in the endothelial nitric oxide synthase gene. *Am. J. Hypertens*. 18(12 Pt 1): 1556–1562.

Moore, K., 2006, Glucose fluctuations and oxidative stress. *JAMA* 296(14): 1730.

Moscow, J., Schmidt, L., Ingram, D., Gnarra, J., Johnson, B., Cowan, K., 1994, Loss of heterozygosity of the human cytosolic glutathione peroxidase I gene in lung cancer. *Carcinogenesis* 15: 2769–2773.

Moskaleva, Elu., Tobolov, I., Shumilov, V., Demina, T., and Gorbunov, E., 1988, Decreased capacity of the peripheral blood lymphocytes for excisional DNA repair in disseminated sclerosis. *Zh. Nevropatol. Psikhiatr. Im S. S. Korsakova*. 88(7): 87–88.

Muschen, M., Warskulat, U., and Beckmann, M. W., 2000, Defining CD95 as a tumor suppressor gene. *J. Mol. Med*. 78: 312–325.

Nair, V., Yuen, T., Olanow, C., and Sealfon, S., 2004, Early single cell bifurcation of pro- and antiapoptotic states during oxidative stress. *J. Biol. Chem*. 279(26): 27494–27501.

Nagata, S. and Golstein, P., 1995, The Fas death factor. *Science* 267: 1449–1456.

Nakajima, T., Elovaara, E., Okino, T., Gelboin, H., Klockars, M., Riihimaki,V., Aoyama, T., and Vainio, H., 1995, Different contributions of cytochrome P450 2E1 and P450 2B1/2 to chloroform hepatotoxicity in rat. *Toxicol. Appl. Pharmacol*. 133(2): 215–222.

Nathan, C., 1992, Nitric oxide as a secretory product of mammalian cells, *FASEB J*. 6: 3051–3064.

Nathan, C. and Xie, Q., 1994, Nitric oxide synthetases: roles, tolls and controls, *Cell* 78: 915–918.

Nouni, H., Rotrosen, D., Gallin, J., and Malech, H., 1998, Two forms of autosomal chronic granulomatous disease lack distinct neutrophil cytosol factors. *Science* 242(4883): 1298–1301.

Oh, G., Pae, H., Lee, B., Kim, B., Kim, J., Jeon, S., Jeon, W., Chae, H., and Chung, H., 2006, Hydrogen sulfide inhibits nitric oxide production and nuclear factor-kappaB via heme oxygenase-1 expression in RAW264.7 macrophages stimulated with lipopolysaccharide. *Free Radic. Biol. Med*. 41(1): 106–119.

Onyango, L. and Khan, S., 2006, Oxidative stress, mitochondrial dysfunction, and stress signaling in Alzheimer's disease. *Curr. Alzheimer Res*. 3(4): 339–349.

Oyama, T., Kawamoto, T., Mizoue, T., Sugio, K., Kodama, Y., Mitsudomi, T., and Yasumoto, K., 1997, Cytochrome P450 2E1 polymorphism as a risk factor for lung cancer: in relation to p53 gene mutation. *Anticancer Res*. 17: 583–588.

Pap, T., Aupperle, K. R., Gay, S., Firestein, G., and Gay, R., 2001, Invasiveness of synovial fibroblasts is regulated by p53 in the SCID mouse in vivo model of cartilage invasion. *Arthritis Rheum*. 44: 676–681.

Parsonnet, J., 1995, Bacterial infection as a cause of cancer. *Environ. Health Perspect*. 103(Suppl 8): 263–268.

Qui, M., Paromov, V., Yang, H., Smith, M., and Stone, W., 2006, Inhibition of inducible nitric oxide synthase by a mustard gas analog in murine macrophages. *BMC Cell Biol*. 30: 7–39.

Ratnasinghe, D., Tangrea, J., Andersen, M., Barrett, M., Virtamo, J., Taylor, P., and Albanes, D., 2000, Glutathione peroxidase codon 198 polymorphism variant increases lung cancer risk. *Cancer Res*. 60: 6381–6383.

Reichmann, E., 2002, The biological role of the Fas/FasL system during tumor formation and progression. *Semin. Cancer Biol*. 12: 309.

Resar, J., Roguin, A., Voner, J., Nasir, K., Hennebry, T., Miller, J. M., Ingersoll, R., Kasch, L., and Semenza, G., 2005, Hypoxia-inducible factor 1alpha polymorphism and coronary collaterals in patients with ischemic heart disease. *Chest* 128(2): 787–791.

Risch, N., 2000, Searching for genetic determinants in the new millennium. *Nature* 405: 847–856.

Ruiz-Ramos, R., Cebrian, M., and Garrido, E., 2005, Benzoquinone activates the ERK/MAPK signaling pathway via ROS production in HL-60 cells. *Toxicology* 209(3): 279–287.

Rossi, G., Cesari, M., Zanchetta, M., Colonna, G., Pedon, L., Cavalin, M., Maiolino, P., and Pession, A., 2003, The T-786C endothelial nitric oxide synthase genotype is a novel risk

factor for coronary artery disease in Caucasian patients of the GENICA study. *J. Am. Coll. Cardiol*. 41(6): 930–937.

Sandrini, A., Johnson. A., Thomas, P., and Yates, D., 2006, Fractional exhaled nitric oxide concentration is increased in asbestosis and pleural plaques. *Respirology* 11(3): 325–329.

Sandström, J., Carlsson, L., Marklund, S., and Edlund, T., 1992, The heparin-binding domain of extracellular superoxide dismutase C and formation of variants with reduced heparin affinity. *J. Biol. Chem*. 267: 18205–18209.

Sandström, J., Karlsson, K., Edlund, T., and Marklund, S., 1993, Heparin-affinity patterns and composition of extracellular superoxide dismutase in human plasma and tissues. *Biochem. J*. 294: 853–857.

Sandström, J., Nilsson, P., Karlsson, K., and Marklund, S., 1994, Ten-fold increase in human plasma extracellular superoxide dismutase content caused by a mutation in heparin-binding domain. *J. Biol. Chem*. 269: 19163–19166.

Schulte-Hermann, R., Bursch, W., Gras-kraupp, B., Torok, L., and Ellinger, A., 1995, Role of active cell death (apoptosis) in multi-stage carcinogenesis. *Toxicol Lett*. 82–83: 143–148.

Semenza, G. L., 2000, Surviving ischemia: adaptive responses mediated by hypoxia-inducible factor 1. *J. Clin. Invest*. 106: 809–812.

Semenza, G. L., 2003, Targeting HIF-1 for cancer therapy. *Nat. Rev. Cancer* 3: 721–732.

Shah, S., 2006, Oxidants and iron in progressive kidney disease. *J. Ren. Nutr*. 16(3): 185–189.

Shen, J., Wang, R., Wang, L., Xu, Y., Wang X., 2004, A novel genetic polymorphism of inducible nitric oxide synthase is associated with an increased risk of gastric cancer. *World J. Gastroenterol*. 10: 3278–3283.

Siebenlist, U., Franzoco, G., and Brown, K., 1994, Structure, regulation and function of NF-κB. *Annu. Rev. Cell Biol*. 10: 405–455.

Soini, Y., Kallio, J., Hirvikoski, P., helin, H., Kellokumpu-Lehtinen, P., Tammela, T., Peltoniemi, M., Martikainen, P., and Kinnula, L., 2006, Antioxidant enzymes in renal cell carcinoma. *Histol. Histopathol*., 21(2): 157–165.

Spoto, B., Benedetto, F., Testa, E., Tripepi, G., Mallamaci, F., Maas, R., Boeger, R., Zoccali, C., Parlongo, R. and Pisano, A., 2005, Atherosclerosis and the Glu298Asp polymorphism of the eNOS gene in white patients with end-stage renal disease. *Am. J. Hypertens*. 18(12 Pt 1): 1549–1555.

Strålin, P., Karlsson, K., Johansson, B., and Marklund, S., 1995, The interstitium of the human arterial wall contains very large amounts of extracellular superoxide dismutase. *Arterioscler. Thromb. Vasc. Biol*. 15: 2032–2036.

Tanimoto, K., Yoshiga, K., Eguchi, H., Kaneyasu, M., Ukon, K., Kumazak, T., Oue, N., Yasui, W., Imai K., Nakachi, K., Poellinger, L., Nishiyama, M., 2003, Hypoxia-inducible factor-1α′ polymorphisms associated with enhanced transactivation capacity, implying clinical significance. *Carcinogenesis* 24: 1779–1783.

Thakali, K., Lau, Y., Fink, G., Gallican, J., Chen, A. and Watts, S., 2006, Mechanisms of hypertension induced by nitric oxide (NO) deficiency: focus on venous function. *J. Cardiovasc. Pharmacol*. 47(6): 742–750.

Thompson, C., 1995, Apoptosis in the pathogenesis and treatment of disease. *Science* 10: 1456–1462.

Trosko, J., Chang, C., Madhukar, B., 1994, The role of modulated gap junctional intercellular communication in epigenetic toxicology. *Risk Anal*. 14(3): 303–312.

Uzel, G., 2005, The range of defects associated with nuclear factor kappaB essential modulator. *Curr. Opin. Allegy. Clin. Immunol*. 5(6): 513–518.

Wang, X. and Wang, J., 2005, Smoking-gene interaction and disease development: relevance to pancreatic cancer and atherosclerosis. *World J. Surg*. 29(3): 344–353.

Warren, W., Biggs, P., El-Baz, M., Ghoneim, M., Stratton, M., and Vebit, s., 1995, Mutations in the p53 gene in schistosomal bladder cancer: a study of 92 tumours from Egyptian patients and a comparison between mutational spectra from schistosomal and non-schistosomal urothelial tumours. *Carcinogenesis* 16(5): 1181–1189.

Weinberg, R., 1991, Tumor suppressor genes. *Science* 254: 1138–146.

Weiss, S., 1986, Oxygen, ischemia and inflammation. *Acta Physiol. Scand. Suppl*. 548: 9–37.
Whitmarsh, A. J. and Davis, R. J., 2000, Regulation of transcription factor function by phosphorylation. *Cell Mol. Life Sci*. 57: 1172–1183.
Wiesman, M. and Halliwell, B., 1996, Damage to DNA by reactive oxygen species and nitrogen species: role of inflammatory disease and progression to cancer. *Biochem. J*. 313: 17–29.
Wu, S., Tan, M., Hu, Y., Wang, J., Scheuner, D., and Kaufman, R., 2004, Ultraviolet light activates NFkappaB through translational inhibition of IkappaBalpha synthesis. *J. Biol. Chem*. 279(33): 34898–34902.
Var, A., Yi;dirim, Y., Onur, M., Kuscu, E., Uyanik, B., Goktalay. K., and Guvenc, Y., 2003, Endothelial dysfunction in preeclampsia. Increased homocysteine and decreased nitric oxide levels. *Gynecol. Obstet. Invest*. 56(4): 221–224.
Verma, M. and Srivastava, S., 2002, Epigenetics in cancer: implications for early detection and prevention, *Lancet Oncol*. 3(12): 755–763.
Vucic, V., Isenovic, E., Adzic, M., Ruzdijic, S., and Radojcic, M., 2006, Effects of gamma-radiation on cell growth, cycle arrest, death, and superoxide dismutase expression by DU 145 human prostate cancer cells. *Braz. J. Med. Biol. Res*. 39(2): 227–236.
Xiao, G. and Li., H., 2006, Effects of inhalation of oxygen on free radical metabolism and oxidative, antioxidative capabilities of the erythrocyte after intensive exercise. *Res. Sports Med*. 14(2): 107–115.
Yang, Q. and Hatton, G., 2002, Histamine H(1)-receptor modulation of inter-neuronal coupling among vasopressinergic neurons depends on nitric oxide synthase activation, *Brain Res*. 955(1–2): 115–122.
Yoshii, Y., Saito, A., Zhao, D., and Nose, T., 1999, Copper/zinc superoxide dismutase, nuclear DNA content, and progression in human gliomas. *J. Neurooncol*. 42(2): 103–108.
You, M., Candrian, U., Maronpot, R., Stoner, G., and Anderson, M., 1989, Activation of the Ki-*ras* protooncogene in spontaneously occurring and chemically induced lung tumors of the strain A mouse, *Proc. Natl. Acad. Sci. USA* 86: 3070–3074.
Yu, Z., Zhou, D., Bruce-Keller, A., Kindy, M., and Mattson, M., 1999, Lack of the p50 subunit of nuclear factor- B increase the vulnerability of hippocampal neurons to excitotoxic injury. *J. Neurosci*. 19: 8856–8865.
Zanetti, M., Sato, J., Jost, C., and Gloviczki, P., 2001, Gene transfer of manganese superoxide dismutase reverses vascular dysfunction in the absence but not in the presence of atherosclerotic plaque. *Hum. Gene Ther*. 12: 1407–1416.
Zelko, N., Mariani, J., and Folz, J., 2002, Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution and expression. *Free Radic. Biol. Med*. 33: 337–349.
Zhang, C., Lopez-Ridaura, R., Hunter, D., Rifai, N., and Hu, F., 2006, Common variants of the endothelial nitric oxide synthase gene and the risk of coronary heart disease among U.S. diabetic men. *Diabetes* 55(7): 2140–2147.
Zornig, M., Hueber, A., Baum, W., and Evan, G., 2001, Apoptosis regulators and their role in tumorigenesis. *Biochim. Biophys. Acta* 1551:F1–F37.