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Mechanism of Lung Carcinogenesis: Electron Transfer, Reactive Oxygen Species, Oxidative Stress and Antioxidants

Peter Kovacic* and Marie-Caline Z. Abadjian

Department of Chemistry and Biochemistry, San Diego State University, San Diego, CA, USA

***Corresponding authors: Peter Kovacic,** Email: pkovacic@sdsu.edu

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Abstract

Lung cancer is one of the most prevalent forms of the illness. Among the various mechanisms proposed, a unifying one involves electron transfer (ET), reactive oxygen species (ROS), oxidative stress (OS), and antioxidants (AOs). The main classes of ET agents are comprised of quinones, aromatic nitro compounds, metallic species, and imine-iminium types. The ROS generated by redox cycling can be beneficial or harmful. Increased levels of ROS are associated with toxicity. In certain cancers, normal cells are mutated by ROS. It is reasonable that AOs can exert favorable effects. This review provides numerous reports which involve ROS-OS in lung cancer, along with studies whereby AOs counter the adverse effects. Examples dealing with the role of various ET metallic compounds involving ROS-OS are presented. Tobacco is a prevalent cause of pulmonary cancer, also with a role for ROS-OS derived from a host of carcinogens in cigarette smoke.

Keywords: Lung cancer; Electron transfer; Reactive oxygen species; Oxidative stress; Antioxidants

Abbreviations: ET: Electron transfer; ROS: Reactive oxygen species; OS: Oxidative stress; AO: antioxidants

Introduction

A prior integrating, mechanistic theme [1] is as follows: A large portion of bioactive substances, including metabolites, utilize electron transfer (ET) processes which are believed to perform vital roles in physiological responses. Groups, such as quinones (or phenolic precursors), metal complexes, aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imine or iminium species, are key players in ET. Redox cycling from such species is depicted in Figure 1. Redox cycling in the presence of oxygen in vivo can lead to oxidative stress (OS) from the formation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide) shown in Figure 2.

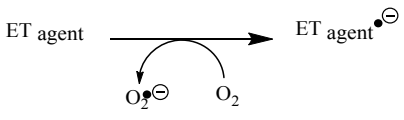

Figure 1: Redox cycling with superoxide formation.

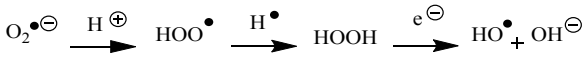

Figure 2: Generation of reactive oxygen species.

In some instances, like respiration or neurochemistry, normal electrical effects are brought about by ET involvement. Bioactive substances with ET groups broadly show reduction potential ranges within the physiologically responsive spectrum (more positive than about -0.5 V). Consequently, the production of ROS from ET in vivo, at low concentration, can be favorable in cell signaling, but at high concentration it can be toxic. Relatively stable radical cations are generated from electron donors, such as phenols, N-heterocycles or disulfides in proteins. The mechanisms of action of drugs and toxins (e.g., anti-infective agents [2], anticancer drugs [3], carcinogens [4], reproductive toxins [5], nephrotoxins [6], hepatotoxins [7], cardiovascular toxins [8], nerve toxins [9], mitochondrial toxins [8], abused drugs [10], pulmonary toxins [11] ototoxins [12] and various other categories [13a]) have increasingly been attributed to ET, ROS, and OS over the past decade.

The ET-ROS theoretical scheme has been receiving mounting acceptance through increasing experimental evidence. The evidence provides data on the generation of the common ROS mentioned previously, e.g. lipid peroxidation, degradation products of oxidation, depletion of antioxidants (AOs), effect of exogenous AOs, and DNA oxidation and cleavage products, and electrochemical data, which supports the ET-ROS scheme. Frequent observations showing a myriad of ET substances present a diversity of activities (e.g. multiple-drug properties) and toxic effects, which is consistent with this comprehensive, unifying mechanism of action.

It is key to acknowledge that the mode of action in the biodomain is generally multifaceted. The ET-ROS-OS mechanism is not the only mode of action; there are other pathways, such as enzyme inhibition, allosteric effects, receptor binding, metabolism or physical factors. For example, protein binding by quinones and amino or thiol nucleophiles effect conjugate addition. Lung cancer is one of the more important illnesses. This review comprises an extension of the prior unifying mechanism based on ET-ROS-OS. The principal carcinogens that fit the hypothesis, either as such or as metabolites, are metal compounds, tobacco and various others. Supporting evidence is based mainly on reduction potentials and generation of ROS-OS. Appreciable literature exists which documents the favorable effects of AOs in countering adverse influence of ROS.

Metal Compounds- ROS-OS

Cisplatin (cis-Pt), Figure 3, is a well-known drug that has been used to combat cancer, including that of the lung [3]. Various mechanisms have been proposed, such as ET-ROS-OS [3]. More recent articles have appeared that add support to the unifying theme. In cis-Pt combination chemotherapy in lung cancer, lipid peroxidation and NO were higher, whereas levels of GSH and SOD were lower, pointing to OS [14]. 4-Methoxychalcone increases OS induced by cis-Pt, as well as cytotoxicity in pulmonary cancer cells [15].

In the case of lung carcinoma, cis-Pt induced the same degree of lipid peroxidation and GSH depletion as did $CoCl_2$ [16], and AO enzymes were activated. Cis-Pt resistant lung cancer cells exhibit higher levels of ROS in comparison to normal cells [17]. There is a relevant review on biometals [18]. Nickel complexes were tested for

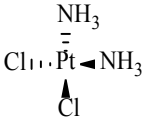

Figure 3: Cisplatin.

cytotoxicity against lung adenocarcinoma [19]. The effect may reflect ROS generation and lipid peroxidation resulting in depletion of the AO pool and DNA fragmentation. Copper complexes were examined as anticancer agents in human lungs [20]. The effects included oxidative damage and mitochondrial dysfunction involving excess ROS.

Treatment of lung cancer cells with arsenic trioxide (As_2O_3) and sulindac enhances ROS and OS [21]. A result was induction of DNA damage. ROS play a role in the As-induced protein kinase activation that is involved in phosphorylation [22]. OS arising from formation of ROS plays an important part. Indium phosphide, extensively used in electronics, was examined as a lung carcinogen [23]. 8-OH αβ expression took place in carcinoma epithelium; the data indicate that inhalation of the indium compound results in lung inflammation related to OS.

Tobacco

Tobacco use is the leading cause of pulmonary cancer [24]. There are reports that AO vitamins may decrease the risk. However, other data gave mixed results. Another study concluded that AO enzymes may modulate the adverse effects [25]. A report found that a combination of dietary AOs provides a beneficial effect [26]. The protective groups comprised carotenoid, flavonoid, vitamin E, vitamin C and selenium. Vitamin E has been implicated in lung tissue repair for pulmonary damage [27,28]. Cigarette smoke induces OS and inflammation which may play a role in pulmonary cancer and COPD [29]. A ROS protein signature was associated with the two illnesses. An OS perspective was used in a study of prototype cigarettes involving lung cancer biomarkers [30]. A review deals with pulmonary cancer in connection with OS, physical activity and nutrition [31]. OS is involved in various physiological processes, such as apoptosis and signaling, in addition to pathogenesis, including lung cancer, aging and degenerative diseases. Physical activity and nutrition appear to provide beneficial effects in lung cancer.

Mechanisms are discussed for OS induced in lung cancer by cigarette smoke [32]. OS can lead to apoptosis, as well as proliferation of lung epithelial cells. Smoking is known to increase lung cancer via free radical reactions [33]. OS levels were higher in smokers in comparison with nonsmokers. Mechanism of tobacco carcinogenesis has been addressed in a prior review [4]. The numerous carcinogens in tobacco make individual mechanisms difficult to study. At least seven nitrosamines and their adducts are present [34]. Certain polycyclic aromatic hydrocarbons found in tobacco such as benzo[a]pyrene (Figure 4), are associated with DNA adduction [35] and DNA damage [36]. Polycyclic aromatic hydrocarbons (PAHs) are known to lead to OS, which in turn affects antioxidant capacity [37].

Favorable redox potentials from cyclic voltammetric studies on conjugated iminium metabolites suggested possible association with ROS via ET to molecular oxygen [38]. Harmful chemicals, such as hydrogen peroxide and superoxide radical anions, are found in cigarette smoke. These ROS cause DNA strand breaks and lipid peroxidation [39,40]. There is evidence of OS by the decreases in glutathione reductase (GSH) and increases in malondialdehyde and 8-OH dG [41].

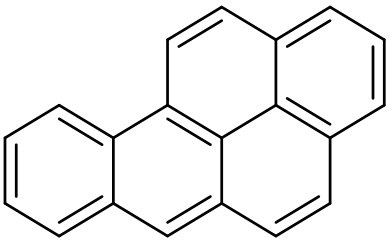

Figure 4: Benzo(a)pyrene.

ROS-OS

There is extensive additional literature that deals with ROS-OS in lung cancer in a variety of ways. OS plays an important mechanistic role in signaling during the anticancer effects [42]. ROS and apoptosis are also involved. Salidroside (Figure 5), a natural glycoside, inhibits cell proliferation and involves apoptosis in lung cancer, which may result from ROS generation and down regulation of an ROS signaling pathway [43,18]. The phenol exerts excellent AO action which may make for a novel therapeutic and preventative agent for OS [33].

The AO property is well known for the phenolic class, e.g., vitamin E [44]. Many illnesses, including lung cancer, result from enhanced production of ROS resulting in OS [45]. Involvement of protein oxidation and pro-oxidant/ antioxidant balance was examined. The Adriamycin drug produced pronounced OS as evidenced by decreasing levels of protective AOs [46]. A report showed that curcumin (Figure 5) produced lung cancer cell apoptosis by way of a mitochondrial route involving ROS [47].

Apoptosis of lung cancer cells is enhanced by depletion of end-binding protein by way of ROS and mitochondrial malfunction [48]. The phenomenon was blocked by N-acetyl cysteine, a scavenger of ROS [49]. In pulmonary cancer, grape seed extract caused OS involving superoxide decreased GSH levels in apoptosis [50]. A study involved OS and genotoxicity by cooking oil fumes in human lung carcinoma [51]. There was oxidative damage to DNA related to ROS generation. Emodin, and anthraquinone (Figure 6) present in rhubarb, generates apoptosis in human lung cancer [52]. ROS are involved via a signaling route in the cytotoxicity.

The AO ascorbic acid blocked the ROS. Generation of ROS in lung cancer cells was enhanced on exposure to pemetrexed (Figure **7**) [53]. This activity is partly mediated through ROS-dependent mitochondrial dysfunction. Erlotinib (Figure **7**), an anticancer drug in the lungs, induced apoptosis, coupled with formation of ROS [54].

Superoxide formation suggests that ROS arise from both mitochondrial and NADPH sources. An article found that estrogen may enhance lung cancer from smoking by women [55]. Estrogen promotes the adverse effects of benzo[a]pyrene involving OS damage.

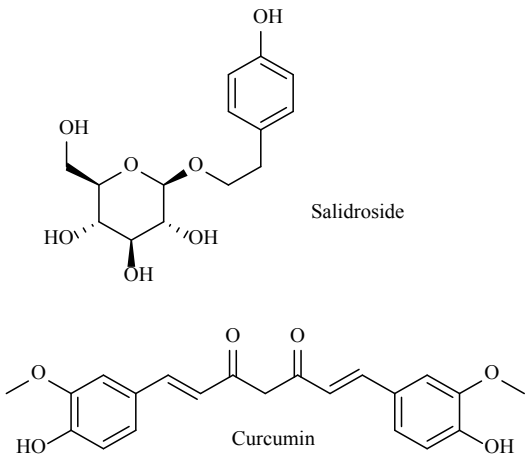

Figure 5: Salidroside and Curcumin.

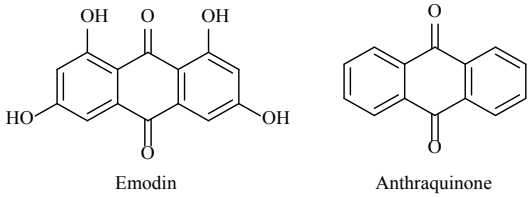

Figure 6: Emodin and Anthraquinone.

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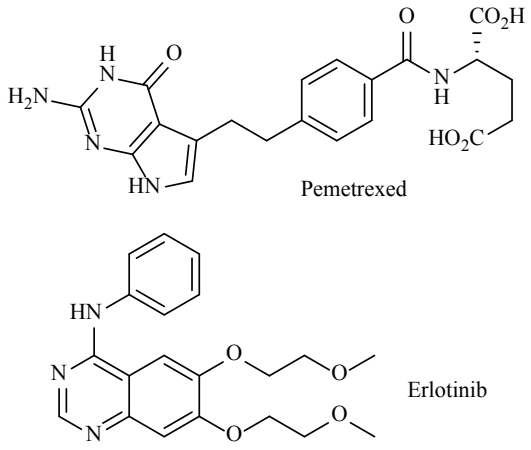

Figure 7: Erlotinib and pemetrexed.

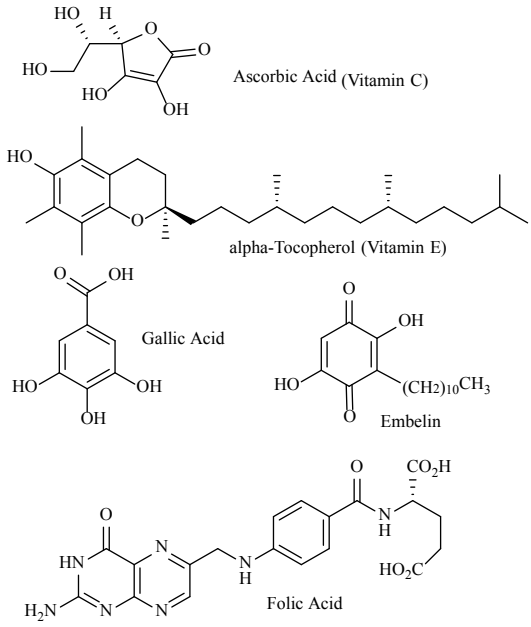

Figure 8: Ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), gallic acid, embelin and folic acid.

Gallic acid (Figure 8) inhibits the growth of lung cancer cells [56]. The effect was accompanied by increase in ROS and decrease in GSH. An investigation deals with anticancer effects in lungs by hecogenin, a natural saponin [57]. The chemical inhibits ROS production and induces cell cycle arrest. Results indicate that with advanced lung cancer, OS increases, whereas AO levels decrease [58]. Enhanced OS is reflected by increase in malondialdehyde and nitrite.

AOs

Relevant discussion is present in prior sections. Various antioxidants have been used to combat lung inflammation and lung cancer (small and non-small cell), such as ascorbic acid, alpha-tocopherol, and embelin (Figure 8). A study involving a relationship between vitamin intake and male lung cancer risk found that ascorbic acid (vitamin C) and folate (Figure 8) might have a protective role against lung cancer in smokers [59,24]. A precursor to carotenoids, beta-ionone has shown antioxidant potential against lung carcinogenesis [60]. A few groups have started tackling the daunting task of making antioxidant indexes, but more research is needed to make a comprehensive index [26,61]. Combined antioxidants have been studied yielding protection against smoke-induced oxidative damage [62] and overall lung function [63,64].

Certain chemicals, like piperine (Figure 9) act as cytoprotective

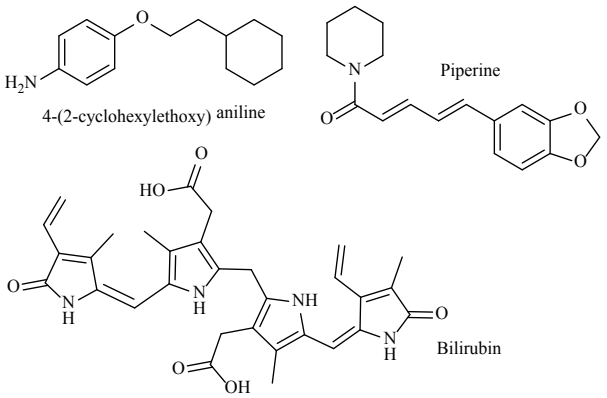

Figure 9: 4-(2-cyclohexylethoxy) aniline, piperine, and bilirubin.

agents that possibly modulate lipid peroxidation and enhance antioxidant activity [65]. Chemotherapeutic agents, such as 4-(2-cyclohexylethoxy) aniline (Fig. **9**) induce apoptosis by generating ROS upon radiation [66]. Flavonoids have interesting efficacy on lung carcinogensis, e.g. hesperidin [67]. Kaempferol, a flavonoid, is another example of involvement in the antioxidant pathway accompanied by apoptosis in non-small carcinoma lung cells [68]. Catechins and derivatives are another source of antioxidants that show protective effects against lung carcinoma cells. Pycnogenol is a pine bark extract that exhibits antioxidant and free radical scavenging properties, decreasing ROS production [69,70]. In low concentrations, an endogeneous antioxidant, serum bilirubin (Figure 9), is associated with lung cancer in smoking related diseases [71]. Serum bilirubin will increase upon cessation of smoking which results in lower risk in lung cancer and cardiovascular diseases.

Other sources of antioxidants include essential oils [72], but more research is needed in this area. Peneciraistin C (Pe-C), a natural spiroketal product, has shown a cytotoxic effect on human lung cancer cells (A549) by inducing cell death and elevating mitochondrial – derived ROS levels [73]. Perfluorooctane sulfonate induces apoptosis in lung cancer cells [74] by a ROS-mediated mitochondrial dysfunction pathway. There is evidence that disruption in the antioxidant balance in metabolism contributes to lung cancer susceptibility [26]. In one study, antioxidant levels and selenium were found to be lower in lung cancer patients compared to the health controls [75]. The important role of selenium as an antioxidant has been shown in a rat study [76].

Conclusions

There is ever-growing experimental evidence suggesting that the unifying mechanistic theme of ET-ROS-OS is involved in lung carcinogenesis. It appears that most lung cancers generated from external toxins such as metal compounds, like tobacco among others, implicate ET agents generating ROS. There is mounting experimental confirmation on the link between ROS and OS supporting this mechanism. The connection between ROS-OS and AOs is also gathering support, as discussed. There is still much research needed to investigate the role of AOs in drug and treatment design.

Acknowledgements

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