International Journal of
Research in Chemistry and Environment
Available online at: www.ijrce.org
ISSN 2248-9649

Review Paper

Molecular Penalties of Cigarette Smoke Induced Human Cellular Oxidative Deregulations

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(Received 18th November 2014, Accepted 19th December 2014)

Abstract: *Cigarette smoke includes numerous precarious chemical molecules, most of them at such low levels that they are imperceptible to their senses. The degree of damage by these compounds is now serious, therefore deciphering the molecular mechanisms underlying cigarette smoke induced oxidative toxicity is one of the major task in modern biology. Now, there is substantial confirmation that cigarette smoke can cause both irreparable changes to the genetic makeup. A vast script pertaining to the toxicological effect of cigarette smoke and other such type of carcinogens has been focused but, mechanisms behind the predisposition and development of oxidative damage to our genetic integrity by cigarette smoke is still mysterious. On this premises we made a current account of consequence of cigarette smoke leading to various molecular upsets leading to oxidative damage and oxidative bust. This mechanistic review will provide an existing supervision of smoke contributing to oxidative damage and molecular alterations confronts assorted human complaints. This fiery knowledge would help in superior sympathetic of better diagnostics, safety assessments, therapeutic strategies and interventions.*

Keywords: Cigarette smoke, DNA damage, Oxidative burst, cellular modulations.

Introduction

After birth and initial life junctures are decisive periods and characterized by severe alterations of the redox balance and by physiological genomic changes in lung cells, which may leads to cancer and other diseases in maturity. Oxidative stress is a major mechanism accounting for the carcinogenicity of cigarette smoke (CS), which becomes more potently carcinogenic, when exposure starts at birth and continues early in life. Data provide evidence that enhanced oxidative stress and the resulting DNA damage and airway inflammation provide a major contribution to the high susceptibility to CS early in life [1, 2].

Smoke is a complex mixture of more than 5,000 compounds including about 200 hazardous chemicals. These chemicals potentially induce various progressive human diseases. Oxidative stress induced by these hazardous compounds in smoke results in pulmonary disease and apoptosis of human airway epithelial (HAE) cells. Nicotine promotes physical addiction to tobacco and also causes pulmonary diseases, cardiovascular diseases or cancers to smokers [3,4]. Ishii (2013) provides evidence that lung is a directly affected organ by cigarette smoking, various respiratory diseases including lung cancer, chronic obstructive pulmonary disease, interstitial lung diseases, bronchial asthma, are caused and worsen by cigarette smoking not only in case of active smoking but also in case of passive smoking. A lot of carcinogen in cigarette smoke causes lung cancer through the DNA damage. Oxidants in cigarette smoke induce airway inflammation and tissue injury [5].

Cellular oxidative burst

Cigarette smoking is a well-known inducer of oxidative stress and observed as a main source of production of exogenous pro-oxidants, reactive oxygen species (ROS) and free radical generators. Smoking raised the ROS production and responsible for the depletion of its scavengers in the circulating blood, this contributing to initiation of oxidative stress. Further, this oxidative stress may direct to cell damage and malfunction through the free radical-mediated

decomposition of vital molecules, such as DNA, proteins and lipids. Conversely, DNA is also a major target of constant oxidative damage from endogeneous oxidants. Although numerous defense systems protect cellular macromolecules against oxidation, there is a high rate of damage to DNA [6-8]. It is investigated that biological damage caused by reactive oxygen species, such as supper oxide radical, singlet oxygen, hydrogen peroxide, and the hydroxyl radical, contributes to aging and various diseases, such as cancer and heart disease. These oxygen species are formed in vivo as byproducts and intermediates of aerobic metabolism and during oxidative stress. Numerous defense systems protect cellular macromolecules against oxidation; nevertheless, there is a high rate of damage to DNA. The oxidized DNA is continuously repaired, and the oxidized bases are excreted into the blood serum and then the urine. It has been observed that chronic cigarette smoking enhanced oxidative DNA damage [9-13].

Recently studies on deleterious effects of cigarette and non-cigarette discharge exposure on acute and chronic modulation of the sympathetic nervous system provide that tobacco smoke lead to increased sympathetic nerve activity, which becomes persistent via a positive feedback loop between sympathetic nerve activity and reactive oxidative species [14]. It is now obvious that cigarette smoking is one of the most injurious and preventable risk factors. However, because of the large composition of cigarette smoke, the detailed mechanisms of generation of various diseases are not fully understood. The studies show that cigarette smoke potently induces DNA cracks, immune modulation, Immune apoptosis and oxidative damage. The generalised view is that cigarette smoke acts as a mutagen and DNA damaging agent in normal epithelial cells, driving tumor initiation. More specifically, study show that cigarette smoke exposure is indeed sufficient to drive the onset of the cancer-associated fibroblast phenotype via the induction of DNA damage, autophagy and mitophagy in the tumor stroma [15].

DNA damage occurs almost all the times in cells, but is repaired also continuously. Occurrence of all these mutations and their accumulation in one cell which finally becomes tumorigenic appears possible, if the DNA repair mechanism is hampered. Cigarette smoke's derivatives like NNK and NNAL are well established carcinogens. 72 enzymes involved in the DNA repair Mechanisms for their interactions with ligands (NNK and NNAL) were analysed. Study indicated the loss of functions of these enzymes, which probably could be a reason for fettering of DNA repair pathways resulting in damage accumulation and finally cancer formation [16].

Cigarette smoking is one of the most important and preventable risk factors for atherosclerosis. Based on controversial reports on the pro-atherogenic activity of cigarette smoke condensate, also called tar fraction (CSC), study carried to analyse the effects of CSC on the viability of endothelial cells in vitro. The show that low concentrations of the hydrophobic tar fraction induces DNA damage resulting in a P53-dependent and BCL-XL-inhibitable death cascade. Higher CSC concentrations also induce apoptotic-like signalling but the signalling cascade is then redirected to necrosis. Despite the fact that CSC induces a profound increase in cellular reactive oxygen species production, antioxidants exhibit only a minimal cell death protective effect [17].

According to the American Thorasic Society (ATS)/European Respiratory Society (ERS) Statement, chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with a strong genetic component, characterized by airflow limitation that is not fully reversible, but is usually progressive and associated with an enhanced inflammatory response of the lung to noxious particles or gases. In susceptible individuals, cigarette smoke injures the airway epithelium generating the release of endogenous intracellular molecules or danger-associated molecular patterns from stressed or dying cells. These signals are captured by antigen presenting cells and are transferred to the lymphoid tissue, generating an adaptive immune response and enhancing chronic inflammation [18].

Previous studies in twins indicate that non-shared environment, beyond genetic factors, contributes substantially to individual variation in mutagen sensitivity; however, the role of specific causative factors (e.g. tobacco smoke, diet) was not elucidated. In this investigation, a population of 22 couples of monozygotic twins with discordant smoking habits was selected with the aim of evaluating the influence of tobacco smoke on individual response to DNA damage. Overall, the results obtained indicate that differences in smoking habits do not contribute to a large extent to inter-individual variability in the response to radiation-induced DNA damage observed in healthy human populations [19].

Cigarette smoke contains numerous compounds that cause oxidative stress and alter gene expression in many tissues, and cigarette smoking is correlated with male infertility. To identify mechanisms by which this occurs, we evaluated expression of antioxidant genes in mouse spermatocytes in response to cigarette smoke condensate (CSC). CSC exposure led to oxidative stress and dose-dependent up-regulation of Hsp90aa1, Ahr, Arnt, Sod1, Sod2, and Cyp1a1 expression in a mouse spermatocyte cell line. An antagonist of the aryl hydrocarbon receptor (AHR)

abrogated several CSC-mediated changes in mRNA and protein levels. Consistent with these results, spermatocytes isolated by laser-capture microdissection from CSC-treated mice showed increased expression of several antioxidant genes. In vivo exposure to CSC was genotoxic to spermatocytes, resulting in apoptosis and disruptions to the seminiferous tubules. Our in vivo and in vitro data indicate that CSC-mediated damage to murine spermatocytes is AHR-dependent and is mediated by oxidative stress [20]. Cheah et al. (2013) investing recently that a major class of chemicals found in tobacco smoke is formed by aldehydes, in particular formaldehyde, acetaldehyde and acrolein. Responses compared of the individual aldehydes with that of the non-aldehydes. Also the response of the aldehydes when present in a mixture at relative concentrations which are present in cigarette smoke studied. Overall, aldehyde responses are primarily indicative for genotoxicity and oxidative stress [21].

Cigarette smoke (CS) is convincingly carcinogenic in mice when exposure starts at birth. It has been investigated the induction and modulation of alterations in the kidney and urinary bladder of CS-exposed mice. Also alter the reprodcutive system via a significant increase in abnormalities affecting epidydimal spermatozoa. Induction of oxidative stress and increase in DNA single- and double-strand breaks in CS-exposed mice, findings suggest that involuntary smoking is potentially able to impair fertility in subjects exposed early in life [22-23].

Concluding Remarks

In light of the literature surveyed the present review will be promising for the social benefit as it would be helpful in deciphering the unknown mechanism of oxidative burst by tobacco exposure for the researchers on one hand and novel therapeutic approaches for the affected individuals on the other. A vast script pertaining to the toxicological effect of cigarette smoke and other such type of carcinogens has been focused on the metabolic activation; DNA breaks leading to transmutation and transformations but, mechanisms behind the predisposition and development of imunne-oxidative damage by tobacco is still mysterious and scanty. Moving ahead, it may also provide substantial help to understand the molecular pathogenesis of disease caused due to chewing tobacco as well as cigarette smoke. Furthermore, it may help in the design the new idea concern about new anti-toxic remedial approach for effective prevention and advance medi-care for long lasting chronic individuals.

Acknowledgement

The work was supported by the Dr. D.S. Kothari Post Doctoral Fellowship Scheme (Award Letter No.: F.4-2/2006(BSR)/13-695/2012(BSR) dated 25 may 2012) grant received from University Grants Commission, Government of India, New Delhi, India.

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