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Review

Oxidation, glycation and glycoxidation—The vicious cycle and lung cancer

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ABSTRACT

The combine effect of oxidative and glycative stress predisposed to glycoxidation, and their outcomes that play critical role in lung cancer have been examined in different ways. The therapeutic approaches for lung cancer are still unsatisfactory. We observe some unclear and decisive pathways which might play an important role in targeting lung cancer. The roadmap of signaling pathway includes p38 MAPK, NF-ƙB, TNF-α and AGE-RAGE binding affinity play role in the cell growth, proliferation, apoptosis inhibition and metastasis. The goal of this review is to achieve a new signaling map inside the lung cancer which is mediated by glycoxidative products mainly reactive dicarbonyls and advanced glycation end products (AGEs). Additionally, AGE-RAGE binding critically regulates the suppression and promotion of lung cancer via inhibition and activation of different signaling pathways. Hence, this review suggests the role of oxidation, glycation, and glycoxidation in lung cancer.

1. Introduction

The continuous accumulation of cellular and molecular changes is the major driving force for the initiation and progression of cancer and recurrence of pathogenic conditions that can be considerably reduced by therapeutically targeting the molecular basis of tumors. It has been estimated earlier that newly diagnosed cancer cases will rise up to 15 million by the year 2020, which may result in 12 million deaths globally [1]. By the year 2016, the cancer incidence was estimated to reach 1.22 million in the Indian population, contributing to 7.8% of the global cancer burden [2,3]. In a broad spectrum of cancer biology, the earlier studies suggest that cancer is predominant among breast, colon, prostate, liver and stomach cancer. The percentage of malignant lung cancer is 13% globally with 6.9% in India [4,5]. A survival rate of only 13% which, does not exceed more than 5 years is observed in patients with lung cancer [3,6]. Lung cancer is characterized by uncontrolled proliferation typically in epithelial cells (carcinomas). The advanced stage of non-small cell lung cancer (NSCLC) may cause death within 18 months of diagnosis [7,8]. The majority of cancer risks, including lung cancer, arise because of uncontrollable factors caused by pollution and toxicants present in the environment, as well as by the free radicals, which cause oxidative stress, which is induced and accumulates because of smoking. These factors contribute to genetic alteration, combined with pollution and toxicants within the environment. Uniquely the inhaled toxic insults to the exposed lungs considered as major factor in case of lung cancer. Cigarette smoke is the main cause of recruiting inflammatory cells consequently inducing altered secretion of inflammatory cytokines predisposes towards lung cancer. A potentate miscreant is immoderate reactive oxygen species (ROS) accumulation due to smoking. These free radicals and ROS, such as $O_2^{\cdot -}$ and H_2O_2, may result from modest leakages from the mitochondrial electron transport chains, endoplasmic reticulum, and chloroplasts. The imbalance between ROS and anti-oxidant defense system leads to oxidative stress within the cell contributes to oxidation of functional biomolecules and ultimately damages the cells, leads to tissue injury [9]. Furthermore, the lung injury triggers chronic inflammation provides microenvironment rich in inflammatory cells mediated cytokines. Cytokines further facilitate oxidative stress burden such as excessive ROS, cell-proliferating growth factors, and other growth-supporting stimuli that enhance tumor initiation. Lung cancer development is triggered

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from oxidant and anti-oxidant imbalance condition created oxidative stress burden. Therefore, inflammation that causes oxidative stress is considered a major precursor or a feature for lung cancer development [10,11].

Furthermore, the morbidity and mortality rates of patients with cancer have rapidly increased worldwide with an increase in diabetes mellitus and diabetes-associated secondary metabolic disorders [12,13]. The confounding risk factors that associate diabetes with cancer are obesity, alcohol, cigarette smoking, high fat and red meat diet [14–17]. Under hyperglycemic and diabetic condition reducing sugars (glucose, fructose) start reacting non-enzymaticaly with proteins, lipids and nucleic acids, altering the structures and functions of these biological molecules by the process known as glycation. Glycation, first described by Maillard in 1912, which is nucleophilic addition of carbonyl group of sugar moiety or reactive dicarbonyls to the amide group of proteins, lipoproteins and nucleic acids [18]. The α-oxaldehydes reactive dicarbonyls mainly methylglyoxal (MG), glyoxal (GO) and 3-deoxyglucosone (3-DG) are the by-products of cellular metabolism under physiological condition. Thus, glycation inevitably produces intermediate reactive dicarbonyl along with the advanced glycation end product (AGE) [19]. These AGEs consist of oxygen and nitrogen containing heterocyclic compounds. The structural and chemical properties of many AGEs still required detailed characterization. They are heterogeneous group of irreversible cross-linked compounds (e.g., pentosidine, carboxymethyllysine [CML] and hydro-imidazolone) that play a role in protein modification and it's cross-linking. The enormous AGEs accumulation in body fluids and tissues often account for toxic AGEs fortifies the pathogenic chain of several deep rooted diseases including diabetes complications, Alzheimer's disease and cancer [20–22]. The abnormal accumulation of AGEs may induce chronic inflammatory response by interacting with multi-ligand cell surface proteins (immunoglobulin super family), called receptor for advanced glycation end products (RAGE). In lungs, the RAGE expression is relatively high as compared to other organs, considered as essential for adult pulmonary homeostasis. The RAGE downregulation is associated progressively with higher stage of tumor in lungs. Thus, RAGE is found to be constitutively expressed in premature, highly expressed in adult lung tissue and down-regulated in cases of NSCLC [23]. RAGE is multiligand pattern-recognition plasma membrane receptor and function by initiating the downstream signaling pathway upon binding to AGEs and several other pro-inflammatory ligands. These ligands other than AGEs including high-mobility group protein B1 (HMGB1), S-100 calcium-binding protein [24,25]. In addition, the RAGE interaction with AGEs activate downstream signaling play decisive role in the progression of a wide spectrum of diseases, such as diabetes, rheumatoid arthritis, nephropathy, neurodegeneration and cancer [22,26]. However, the underlying mechanism of RAGE and pro-inflammatory ligand binding resulting in RAGE activation promote the sustained activation of pro-inflammatory transcription factor nuclear factor kappa B (NF-κB), p38 mitogen-activated protein kinesis (MAPK), tumor necrosis factor–α (TNF-α) [27–29]. These factors further plays vital role in stimulating cell-proliferating growth factors and suppress a series of endogenous autoregulatory functions. In case of renal cell carcinoma, the TNF-α activated NF-κB pathway promote tumor cell proliferation, inhibition of apoptosis, increases the tumor angiogenesis ability and the potential of tumor cell invasion and metastasis [30]. Therefore, it seems necessary to correlate between glycation and oxidation i.e. glycoxidation. Glycoxidation is a combinational effect of both oxidation and glycation that generates AGEs and is involved in diabetes and secondary complications associated with this metabolic disorder, including cardiovascular diseases, Alzheimer's disease and nephropathy in addition to various forms of cancer [31]. Under oxidative stress, the process of lipid peroxidation induce MG and GO which further involves in glycoxidation leads to the formation of AGEs. Further, AGE-RAGE axis trigger intracellular signaling pathway leading to the activation of signaling cascade which targets the growth and apoptosis related genes [32,33]. Therefore, the regulated expression of genes promote cell proliferation and apoptosis may up and downregulate the progression of lung cancer [34–37]. With the increase in the number of lung cancer cases, it must be found out the therapeutic targets for lung cancer treatment might have some positive hypothesis when linked with glycoxidation. The up and down regulation of different signaling pathway genes correlated with glycoxidative stress mediated progression of lung cancer might provide ascertain therapeutic targets for medicinal development in the very near future.

2. Possible mechanism of oxidation and glycation associated with the lung cancer

The basic features of cancer are distinctive. The complementary capabilities that enable the occurrence of cancer and its progression in all forms depend on the types of inflammatory pathways that produce free radicals such as ROS ($O_2^{\cdot -}$, H_2O_2, and $OH^{\cdot}$), implicated that how normal cell generation evolves progressively to exhibit neoplastic state [38,39]. The initiation of many tumors and cancers including lung cancer arises due to the deleterious effect of free radicals which shoots up over the period of years. Inflammation in lungs directly causes mutation, DNA damage and strike intra/extra cellular functional proteins and lipoproteins by activating enzymes such as flavin monoxygenases (FMO), cytochrome P-450 oxidase (CYP-450) that produce a large quantum of ROS in the cells, finally paralyzing the cellular machinery to mitigate with oxidative burden [40,41]. Oxidants that are inhaled by smoking cause cellular damage by directly targeting proteins, lipids, nucleic acids and by depleting the level of anti-oxidants, thereby disturbing oxidant/anti-oxidant balance in the lungs, increases oxidative styress promote lung injury [42]. Among the mainstream biomolecules (DNA, lipids, and proteins), proteins are more abundant in the body and show specific reactions with several other molecules. Thus they are the major target of biological oxidants and free radicals. Therefore, ROS production at a high level mainly results in protein damage, both in the intra- and extracellular matrix of the cell. Hence, it is necessary to recognize the factors that control a protein's reactivity toward biological oxidants from both a biomedical and bio-processing point of view [9]. The synergistic action of high level of ROS increases protein oxidation, auto-oxidation of sugars and lipid peroxidation. Furthermore, the lipid peroxidation contribute to generates a variety of reactive carbonyl species (RCS) which include aldehydes and α-oxaldehydes by the oxidation of polyunsaturated fatty acids (PUFA). Reactive aldehydes include 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA). 4-HNE and MDA react with amino acids such as lysine (Lys), histidine (Hys) and arginine (Arg) residues of intra and extracellular proteins and lipoproteins, forming schiff's base. This schiff's base underwent rearrangement to form protein and lipo-proteins aggregates known as AGEs and advanced lipoxidation end product (ALEs). Similarly, dicarbonyls such as MG and GO from lipid peroxidation again react with proteins and lipoproteins which trigger further glycation and glycoxidation reaction [31,35,43].

On the other hand, glycative stress is the foremost biological consequence of glycation comprise uncheck oxidative stress and chronic inflammation which are also concealed constituents of tumor growth and cancer onset. As discussed above, the non-enzymatic glycation of proteins is a post translational process which occurs in tissues and body fluids, usually associated with hyperglycemic and oxidative stress conditions [44,45]. The covalent bonding between carbonyl group of reducing sugars or MG and GO to the free amino groups of protein result in the formation of reversible schiff's base, and the later undergoes rearrangement, dehydration and cyclization to form a more stable Amadori product (Ketoamines) that further directly initiates the formation of highly reactive dicarbonyl intermediates MG and GO which can further exert glycative stress. MG is formed by the fragmentation of triosphosphate glyceraldehydes-3-phosphate and di-hydroxyacetone phosphate (DHAP) whereas GO is a byproduct of glycerolipid. MG is