World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

PERCIPIENCE OF BIOLOGICAL MECHANISMS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS RISK OF LUNG CANCER

Akhila Yerubandi*, Sivakshari Makkapati, Sreenu Thalla, Padmalatha Kantamneni

Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh, India, 521108.

***Corresponding Author: Akhila Yerubandi**
Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh, India, 521108.

Article Received on 05/01/2020 **Article Revised on 26/01/2020** **Article Accepted on 16/02/2020**

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is defined as the chronic lung disease which is progressive and irreversible obstruction of airway along with the episodes of acute exacerbations. It is a combination of Emphysema and Chronic Bronchitis. Lung cancer has become most leading cause of death in last few years. Squamous cell carcinoma is the COPD related type of cancer, which is most common type of lung cancer. COPD is the major health hazard affecting around 251 million people globally. Biological mechanisms include chronic inflammation, Oxidative stress and DNA damage and repair. Genetic mechanisms include genetic overlap, somatic mutations, DNA methylation, MicroRNA (miRNA) regulation and epigenetics. Formation of lung tumor is due to induction of various interleukins and cyclooxygenase -2. Oxidative stress has major role in lung cancer development. Reactive Oxygen Species (ROS) damages DNA and single strand breaks and sites are increased in COPD and the lung cancer. Somatic mutations may affect both lung cancer and COPD. Hyper methylation of both promoter and tumor suppressor genes occur in lung cancer. miRNA regulates about more than 60% of protein coding genes. DNA methylations and post-translational modifications of histones are observed in these changes. Biological mechanisms identified so far offers a target for development of particular therapeutic strategies that further improve the health of the patients.

KEYWORDS: Chronic Obstructive Pulmonary Disease, Lung cancer, Biological mechanisms, Genetic mechanisms.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as the chronic lung disease which is progressive and irreversible obstruction of airway along with the episodes of acute exacerbations. It is a combination of Emphysema and Chronic Bronchitis.[1] Few studies explained that COPD is going to be the third leading cause of death in 2020. COPD has about 25% of the life time risk. The major risk factor of COPD is smoking where 20-25% of smokers develop COPD. If the inflammatory response starts in COPD, it only persists after cessation of smoking.[2] This inflammation may leads to two major manifestations that includes cardiovascular disease (CVD) and lung cancer. Few studies suggest that there is a strong association that inflammatory process of COPD increases the risk of CVD and lung cancer.[3]

Lung cancer has become most leading cause of death in last few years. The major etiological factors of COPD are smoking and occupational exposures such as pollution, biomass exposure, industrial dust and fuels exposure, asbestos and radiation.[4] There were various epidemiological studies conducted in 1950's and 1960's in which association of lung cancer and cigarette smoking were clearly established. Molecular epidemiology mainly focuses on the biological mechanisms that develop the malignancy in lung parenchyma and airways of smokers and the factors that develops lung cancer. COPD which is one of the major cause of morbidity and mortality have more risk of lung cancer.[5] A study explains that patients with moderate to severe COPD have more risk of developing lung cancer five times more than that of cigarette smokers without disease. The major mechanisms that progress various lung diseases such as COPD, Emphysema and Lung disease has gained much attention from past few years. Oxidative and Nitrosative stress results in reactive oxygen and nitrogen species (ROS and RNS) that activates the cellular process results in neoplastic transformation or the mutations in DNA induction which finally favors carcinogenesis.[6]

Even a small reduction of forced expiratory volume in Cyclooxygenase -21 second (FEV1) acts as marker for airway obstruction and a predictor of lung cancer. COPD patients have risk of lung cancer with an average duration of 14.5 years follow up. Squamous cell carcinoma is the COPD related type of cancer, which is most common type of lung cancer.[7]

Epidemiology

COPD is the major health hazard affecting around 251 million people globally. Presently, COPD is affecting around 8-10% of adults and 15-20% of smokers in the world. Cancer related mortality is having high rate for lung cancer. An estimate of 10 million deaths per year are due to lung cancer by 2030.[1] Around 90% of cases of COPD are due to tobacco smoking. Out of these 90%, around 70-80% has the risk of lung cancer. Particulate matter exposure in air increases the risk of lung cancer by 14%. In a study, about 50-70% of patients having lung cancer had the spirometric evidence of COPD.[5]

Biological Mechanisms

Chronic Inflammation

Formation of lung tumor is due to induction of various interleukins and Cyclooxygenase-2. Activated leukocytes releases free radicals, proteases that combine with tertiary lymphoid aggregates which results in development of tumor in COPD patients.[3] Other mechanisms involved are apoptosis, autophagy, angiogenesis and cell repair mechanism. Migration of non-small cell lung carcinoma (NSCLC) cells A549 are increased in serum samples of COPD patients.[4] There are increased levels of cytokines such as Chemokine (C-C motif) ligand 21 (CCL - 21), C-X-C motif chemokine 12 (CXCL 12) but not C-X-C motif chemokine 15 (CXCL 15) in the serum samples of patients when compared to control group. Inhibition of CCL - 21, CXCL 12 increases the migration of A549 cells in COPD patients. This is medicated by former cytokine CCL - 21.[6] There fore few studies suggests that CCL - 21 favors the cancer cell migration in the lungs of COPD patients. Other cytokines and growth factors include tissue necrosis factor alpha (TNF - α), Vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF – β) that develops lung cancer.

T cells play various roles in the development of tumor. T-helper cells -1 (Th1 cells) releases TNF - α, Interleukin 2 (IL 2), Interferon gamma. These show anti tumor effects. T-helper cells -2 (Th2 cells) releases interleukin 4 (IL 4), which favors the growth of tumor cell and inhibits the host immune system. In lung cancer, Th1 cells are decreased and Th2 cells are increased.[2] After surgery, these levels of Th1 and Th2 cells are modified in same patients. Interleukin 10 (IL 10), interleukin 14 (IL 14) are decreased after surgery than before surgery. Th1 cells are more in Lung cancer patients with COPD than in those patients without COPD. Interleukin 17C (IL 17C) increases the neutrophil recruitment that enhances the inflammation in tumor cell and there by promotes tumor cell growth.

Macrophages play a key role in pathogenesis of COPD.[3] Polarized macrophages show pro inflammatory and anti-inflammatory response based on cytokine secretions. There are 2 subtypes of macrophages such as type 1 (M_1) and type 2 (M_2) plays role in tumor cell growth. Tumor cell growth is promoted by regulation of various functions such as cell death, cell repair and cell adhesion. M_1 cells enhance inflammation and fight against tumor cells. M_2 cells show anti-inflammatory actions, repairs tissue and promote cancer cell growth. In COPD patient with no lung cancer, M_1/M_2 classic pattern was not followed. A study reported that M_1 cells are decreased and M_2 cells are increased in diseased patients samples.[5] Increase in M_1/M_2 ratio in patients with lung cancer with COPD than in patients with lung cancer without COPD concludes that prognosis of patients with lung cancer with COPD is better when compared to patients without COPD.[7]

Oxidative Stress

Oxidative stress amplifies the inflammatory response and loss of Nrf2 function in COPD patients contributes to the enhanced susceptibility of COPD patients to lung cancer through regulation of expression of various anti oxidants and detoxifying enzymes and results in enhancement of lung inflammation. Somatic mutations in DNA can also be induced by oxidative stress.[4] It may form 80hydroxy-2-deoxyguanosine residues and affects the DNA methylation. Reactive nitrogen and oxygen species (RNOS) are the major source of inflammation that is elevated in COPD patients. RNOS are present in mitochondria, which is dysfunctional in COPD patients. Oxidative stress has major role in lung cancer development.[8] RNOS damages DNA and inhibits the function of DNA repair genes. It also increases the expression of DNA methyltransferases. Reactive Oxygen Species (ROS) are produced by the addition of electrons to oxygen molecule. Oxidative Stress occurs as a result of an imbalance between the oxidants and anti oxidants in the cells and tissues. Oxidative damage to the cellular components of the cell is induced through various mechanisms such as Peroxidation of membrane phospholipids, modifications of nuclear DNA and alterations in proteins or cell proteins oxidation.[9]

DNA Damage and Repair

Reactive Oxygen Species (ROS) damages DNA and single strand breaks and sites are increased in COPD and the lung cancer. Oxidative stress and DNA damage are increased in COPD patients with biomass exposure. Increase in DNA damage is not only due to cigarette smoking and increased double stranded breaks in the lungs of COPD patients when compared to smoker, non-smokers without COPD.[7] Direct repair, base excision repair, nucleotide excision repair, cross link repair and double strand break repair are the various mechanisms of DNA repair. The efficient repair of DNA double strand

breaks can maintain chromosomal integrity. A study suggests that in diseases like COPD, there is decrease in HDAC 2 and SIRT 1 expression and there may be less protection against DNA breakage and repair promoted by environmental factors increasing the potential for the somatic mutations and the risk of lung cancer.[10]

Genetic Mechanisms

Genetic Overlap

An overlapping gene is a gene of expressible nucleotide sequence that partially overlaps with expressible nucleotide sequence of another gene. Genome wide association study (GWAS) suggests that lung cancer have associations with the various loci of the gene and some of these loci are susceptible to COPD. The pathogenic feature of COPD, lung cancer and inflammation is Epithelial mesenchymal transition (EMT).[2] The genotype rs7326277TT in VEGFR1 enhance the process of tumor growth and acts as susceptible loci for both the diseases. Polymorphisms in anti-inflammatory gene IL 10 shows the increased risk of COPD and lung cancer.[4] Overlapping loci at chromosome 15q25 and 4q31 in both COPD and lung cancer are identified in early GWAS. Locus at chromosome 15q25 is susceptible to the COPD but loci at chromosome 4q31 was associated with the decreased risk of COPD and lung cancer that is not dependent on COPD.[5]

Somatic Mutations

Somatic mutations may affect both lung cancer and COPD. In patients with lung cancer and smokers, there are acquired mutations in Phosphatase and tensin homologue (PTEN) and tissue protein 53 (TP53), epidermal growth factor receptor (EGFR) and Ras. PTEN, PT 53 are the well characterized tumor suppressor genes.[1] These mutations result in loss of functions in PTEN and TP 53 and gain of functions in EGFR and Ras. Further more mutations in EGFR with tyrosine kinase play a role in lung cancer. There is a link between somatic mutations and pathogenesis of COPD based on early evidence.[3] In the epithelium of smokers and COPD, signaling of Nuclear factor kappa B (NF kB) and activator protein - 1 (AP - 1) are unregulated. These signals mediate the expression of the inflammatory proteinases and cytokines in response to the oxidative stress.[4]

DNA Methylations

By addition of methyl group to 5' position of cytosine residue of DNA structure called as DNA methylation and this modification is reversible. This process is a part of cluster of tumor suppressor genes that promote the proliferation.[4] DNA methylation in COPD is attributed to hypo methylation of the immune modulatory genes such as SERPINA1 that encodes alpha1-antitrypsin results in gene over expression. Hyper methylation of both promoter and tumor suppressor genes occur in lung cancer.[6] As DNA methylation differentiates the smokers, COPD and also subtypes of carcinoma, it has potential role as biomarker for diagnosis and treatment of the disease. Regression of genes CCDC37 and MAP1B and DNA methylation were reported to be more prevalent in patients with lung disease and COPD when compared to patients without COPD in aepigenome wide association study. In a study, higher degree of methylation is observed in lung cancer patients than in COPD patients.[9]

MicroRNA (mi RNA) Regulation

mi RNAs are epigenetic mediators and small non coding RNAs that regulates the protein expression through synthesis or translation. This acts as key control of various functions or physiological processes such as proliferation of cells, differentiation and apoptosis. This is involved in post transcriptional regulation by the degradation of target mRNA.[8] miRNA regulates about more than 60% of protein coding genes. This also acts as the tumor suppressors or oncogenes. A study explained that down regulation of miR-218-5p in lung tissue of COPD patients when compared with non-smokers and was also correlated with the severity of airway obstruction. This also acts as a biomarker for both carcinoma and COPD.[10] SNPs affect the expression, sequence, target site binding, epigenetic alterations of miRNA. More Cyclooxygenase - 2 (COX - 2) is produced from fibroblasts of COPD patients and its product prostaglandin E2 (PGE 2) is also more when compared to healthy smokers. miR-146a regulates the COX - 2 expression that is promoted by the fibroblast stimulation.[10]

Epigenetics

Gene and DNA expressions are altered without any alterations in DNA sequence and these heritable changes are known as epigenetic modifications. DNA methylations and post-translational modifications of histones are observed in these changes. This controls the chromatin structure and remodeling that finally controls the cells translational outcome.[4] DNA promoter hyper methylation, Post translational modification of histone, DNA global hypo methylation and miRNA silencing by DNA hyper methylation are the major epigenetic alterations associated with the lung disease. A study suggests that there is association between the cigarette smoke and the cancer associated with the epigenomic alterations in the cultured respiratory epithelium.[5]

CONCLUSION

COPD is associated with systemic inflammation with various biological mechanisms. Most of the COPD patients have the risk of developing lung cancer mostly the non- small cell lung carcinoma. There is high risk to the COPD patients with a habit of cigarette smoking.[1] There is strong evidence from many studies that the inflammatory mediators in COPD are related to the development of lung cancer.[4] The mechanisms that link the COPD with the co morbidities such as lung cancer and CVD are not clearly defined due to the lack of established experimental models. The potential area to

undergo more studies is to find out the particular factors that develop inflammation in COPD.[7] Biological mechanisms identified so far offers a target for development of particular therapeutic strategies that further improve the health of the patients.[9]

ACKNOWLEDGEMENT

We acknowledge the Vijaya Institute of Pharmaceutical Sciences for Women for support and valuable guidance.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Paul T King, Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer, Clinical and Translational Medicine, 2015; 4(26): 01-13.
2. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary, American Journal of Respiration and Critical Care Medicine, 2012; 187: 347–365.
3. Mannino DM, Buist AS, Global burden of COPD: risk factors, prevalence, and future trends, Lancet, 2007; 370: 765–773.
4. Esther Barreiro, Victor Bustamante, Victor Curull, JoaquimGea, Jose Luis Lopez-Campos, Xavier Munoz, Relationships between chronic obstructive pulmonary disease and lung cancer: biological insights, Journal of Thoracic Disease, 2016; 8(10): 1122-1135.
5. Vlahos R, Bozinovski S, Role of alveolar macrophages in chronic obstructive pulmonary disease, Frontiers in Immunology, 2014; 5(435): 1-7.
6. Kasala ER, Bodduluru LN, Barua CC, Antioxidant and antitumor efficacy of Luteolin, a dietary flavone on benzo (a) pyrene-induced experimental lung carcinogenesis, Biomedicine and Pharmacotherapy Journal, 2016; 82: 568-77.
7. A.L. Durham, I.M. Adcock, The relationship between COPD and lung cancer, Lung cancer, 2015; 90: 121-127.
8. Ian M. Adcock, Gaetano Caramori, Peter J. Barnes, Chronic Obstructive Pulmonary Disease and Lung Cancer: New Molecular Insights, Respiration, 2011; 81: 265-284.
9. Brielle A. Parris, Hannah E. O Farrell, Kwun M. Fong, Ian A. Yang, Chronic obstructive pulmonary disease (COPD) and lung cancer: common pathways for pathogenesis, Journal of Thoracic Disease, 2019; 11: 2155-2172.
10. LonaZeneyedpour, Lennard J. M. Dekker, Jenny J. M. van Stenvant Hoff, Peter C. Burgers, Nick H. T. ten Hacken, and Theo M. Luider, Neoantigens in Chronic Obstructive Pulmonary Disease and Lung Cancer: A Point of View, Proteomics Clinical Applications, 2019; 13: 01-07.