International Journal of Experimental Research and Review (IJERR)

ISSN: 2455-4855 (Online) ***Review Article***
Received: 12th November, 2020; **Accepted:** 17th December, 2020; **Published:** 30th December, 2020

DOI: https://doi.org/10.52756/ijerr.2020.v23.002

A brief review on cigarette induced cellular damage

Sudip Dey[1] and Pokhraj Guha[1*]

*Department of Zoology, Garhbeta College, West Midnapore, West Bengal, India

[*]**Corresponding Author:** pokhraj.pg@gmail.com

Abstract

Cigarette smoking has become one of the most common addictions in context to the present scenario of tobacco consumption. Comprising of nearly 7000 chemicals, cigarette smoke have both free radicals and oxidizing agents in both smoke tar and gas phase, both of which can cause oxidative stress in human health. Long time smoking causes decreased serum immunoglobulin level but increased level of auto–antibodies. During chronic oxidative stress resulting from cigarette smoking, cells secrete mucus and increased viscosity of mucus in airways makes it susceptible to bacterial infection. Furthermore, chronic exposure of lungs to tobacco smoke causes unfolded protein response, ER stress and altered ceramide metabolism. Apart from the above mentioned facts, Cigarette smoking can also cause senescence resulting in abnormal wound healing that exaggerates pathogenesis of COPD. Although there are several management therapies available for COPD management, but the permanent cellular damages due to smoking are irreparable and results in disease exaggeration and suffering.

Keywords: Auto-immune disease, oxidative stress, ROS.

Introduction

Smoking is the practice of inhaling and exhaling smoke of tobacco. Cigarette is tobacco filled long thin paper tube. In today's society smoking cigarette is a common practice. In spite of knowing that it has many adverse effects on our body, there are about 1.3 billion smokers in our world and the number is gradually increasing. Smoking is highly addictive and it is the reason why many people do not quit smoking. Tobacco contains nicotine which causes a rush of Adrenalin, it also trigger dopamine-Brain's happy chemical. Nicotine has many harmful effects like suppression of appetite, increases blood sugar, disruption of metabolism (Mishra et al., 2015). Separate study on male and female twins by the Medical College of Virginia and St. Louis University shows that nicotine addiction is more genetic influence than environmental influence. When people smoke cigarette about 7000 chemical enter in their body, which has severe destructive effects on body, moreover it is also found that many of its component is carcinogenic (Hecht, 1999). The chemicals of cigarette rapidly absorbed in cells and affects from internal functioning to

efficiency of immune system. Smoking cigarette not only causes cancer but also several lung diseases such as Asthma, COPD, Chronic Bronchitis and Emphysema, Lung cancer etc. (Saha SP et al., 2007).

Composition of Cigarette smoke

Cigarette smoke (CS) is a complex mixture of more than 7,000 chemicals including different low-molecular-weight carbon- and oxygen centered radicals, Polyaromatic Hydrocarbons (PAHS), certain Tobacco-Specific Nitrosamines (TSNAs), Carbon Monoxide (CO), Hydrogen Cyanide (HCN), and Nitrogen Oxides etc. Which have various carcinogenic, mutagenic and toxic effects (Church and Pryor, 1985). TSNAs like Nicotine-derived Nitrosamine Ketone (NNK), N-nitrosonornicotine (NNN) have much carcinogenic effect, other TSNAs are N'-nitrosonatabine (NAT), N'-nitrosoanabasine (NAB) (Leigh et al., 2018). Cigarette smoke has two parts - the gas phase smoke or main stream smoke which contains about 99.9% of materials and another is tar which is the material retained in filter.

Tar and gas phase both have free radical and highly oxidizing agent, approximately 10^{17}oxidizing molecule is present in cigarette per puff (MacNee, 2005) putting body in oxidative stress. Tar phase radicals are organic and stable whereas gas phase radicals are organic and inorganic including ROS, peroxide, nitric oxide, and other free radicals. Tar phase has semiquinone, hydroxyl radical (.OH) and hydrogen peroxide (H_2O_2).

Cigarette smoke and its effect on Cellular system

Cigarette smoke has major harmful impact on cellular system. It hampers immune system, causes premature death of cells, and causes oxidative stress on cell.

1. Effect of Cigarette smoke on body Immune system

Many pathogen and harmful chemicals expose body through the lungs route and lungs have specific and non-specific mechanism for clearing the invaders from lungs. Continuous cigarette smoking compromises body immune system, both innate and adaptive - which are involves in protection of lungs from harmful invaders. Adaptive immune components-T helper cells (Th1/Th2/Th17), CD4+CD25+ regulatory T cells, CD8+ T cells, B cells and memory T/B lymphocytes affected due to smoke and in case of innate immune system, DCs, NKs and Macrophages got affected (Qie et al., 2017). Cigarette smoking increases the number of alveolar macrophages which is important parts of innate immunity along with other monocytes. Alveolar macrophage (AM) secreting elevated level of lysosomal enzymes and Elastase (Sopori, 2002; Reynolds, 1987), usually making damages in parenchymal and epithelial cells of lungs that contribute pathogenesis in COPD. AM secretes some pro-inflammatory cytokines which are important for body defense system and in smokers this cytokines are decreased (Kishimoto, 1989; Beutler, 1990).Cigarette smoke has severe impact in molecular pathway like histone modification, MAP kinase, NF-κB. (Qie et al., 2017). Chronic inhalation of cigarette smoke in rat has increased chances to develop lung tumors (Dalbey et al., 1980). Long time smoking causes decreased serum immunoglobulin (Ferson et al., 1979) level but increased level of auto — antibodies (Mathews et al., 1973; Masdottir et al., 2000). Smokers are more susceptible to bacterial infection (Takeuchi et al., 2001).

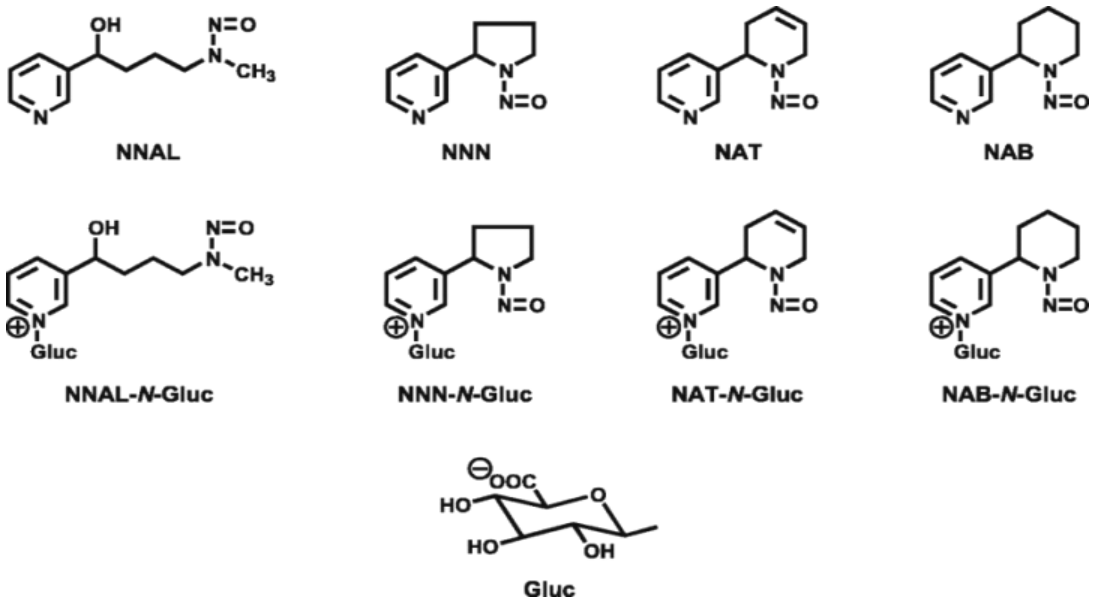

Figure 1. Different TSNAs (adopted from Stepanov et al., 2005).

2. Cigarette smoke and Oxidative stress

Oxidative stress is defined as the imbalance between free radicals and antioxidants in body. Disturbance in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that causes DNA damage, protein damage, lipid peroxidation which has role on cancer, aging, cardiovascular diseases. Cigarette smoke induces oxidative stress and causes inflammation in lung tissue in both in vivo and in vitro conditions. Short lived radicals quenched immediately in epithelial lining fluid (ELF). Redox reaction of cigarette smoke generates ROS. Producing ROS is common as many biochemical reactions causes ROS as a byproduct but inhaling cigarette causes drastic increase of ROS, putting body in oxidative stress which is related to various lung diseases, carcinogenesis, inflammation etc.

In oxidative stress pro-inflammatory cytokines (TNF-α, IL-1, and IL-8) are produced from lung cells that are able to induce neutrophil recruitment and activation of transcription factors such as activator protein-1 (AP1) and nuclear factor-κB (NF-κB) (Rahman and MacNee, 1998).

In chronic oxidative stress, cells secrete mucus and increased viscosity of mucus in airways makes it susceptible to bacterial infection. Moreover, chronic exposure of smoke in lungs causes unfolded protein response, ER stress and altered ceramide metabolism. Though in healthy glutathione-dependent detoxification and anti-oxidant enzymes (nuclear factor erythroid 2-related factor 2 pathway is main for anti-oxidation pathways) increases, in COPD patient Nrf2 response is defective.

Oxidative stress causes ER stress and it leads to unfolded protein response (UPR). Cigarette smoke induces expression of protein kinase R-like endoplasmic reticulum kinase (PERK)-dependent bZip transcription factors (Kelsen et al., 2008). Decrease in protein synthesis due to phosphorylation of eukaryotic Initiation Factor (eIF) 2-α by PERK is another factor in allowing cells to survive (Cullinan and Diehl, 2006).

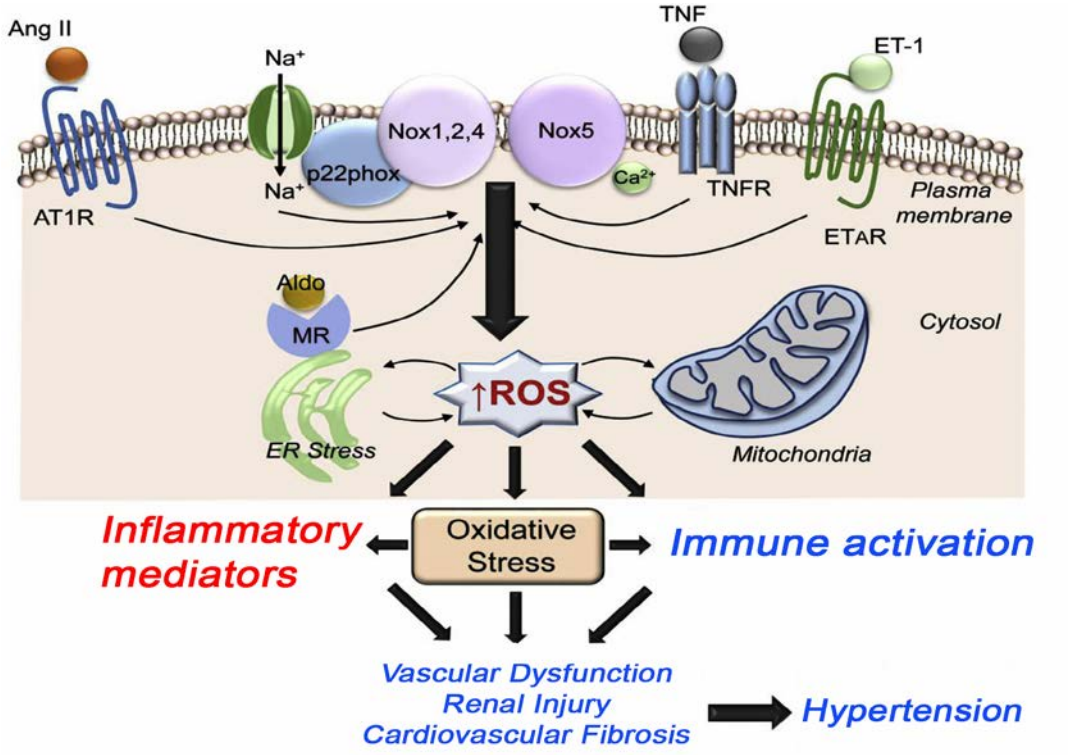

Figure 2. Free radical toxicity.

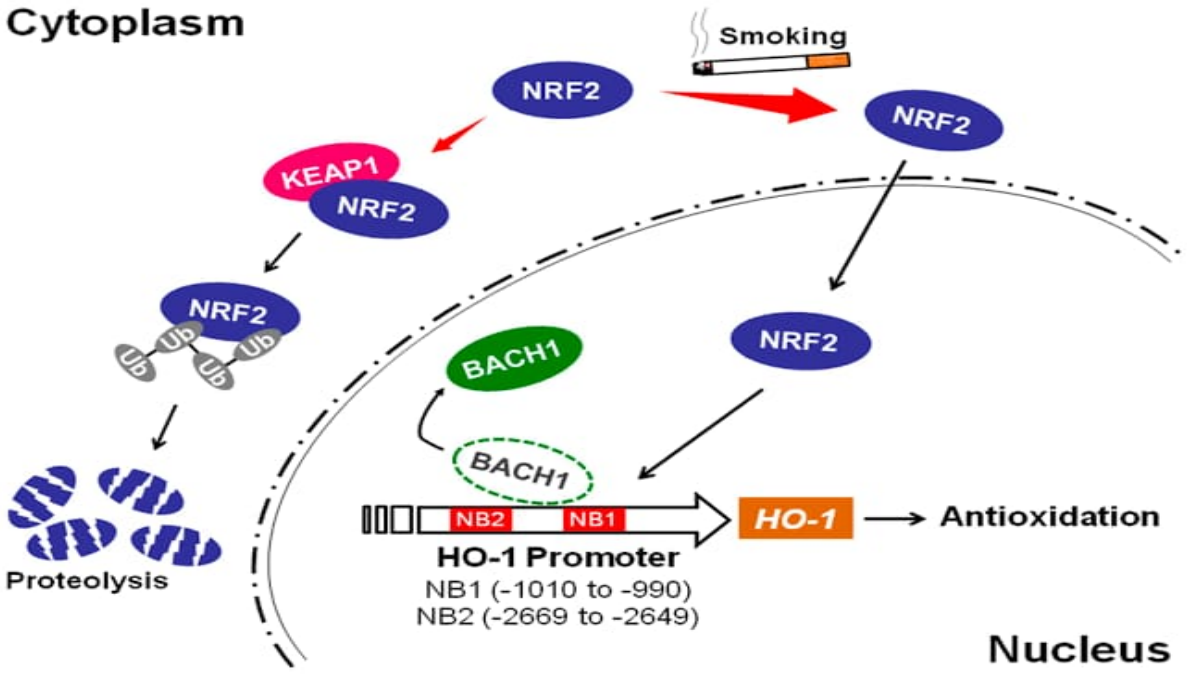

Figure 3. NRF2 pathways (Adopted from Chang et al., 2017).

3. Effect of cigarette smoke on cellular system

Cigarette smoke has much adverse effects on cellular system. Chemicals that is present in cigarette cause cell damage and inflammation, loss of interstitial matrix, protease–antiprotease imbalance. In case of cigarette smokers — chemicals released from cigarette causes oxidative stress in pulmonary cells and AM. Eventually they started to over produce pro-inflammatory cytokines and chemokines and other growth factors (Rutgers et al., 2001).

The persons with chronic inhalation of smoke have elevated level of WBC as body try to heal the injury causes by cigarette smoke. Apoptosis or programmed cell death, necrosis and anoikis are the processes by which lung tissue of COPD patient (Yoshida, 2003; Tuder, 2007). Apoptosis is programmed cell death which is mediated by different Caspases, though it is a harmful process causing loss of critical cell populations, it provides an alternative route for necrotic death of injured tissues. (Henson and Tuder, 2008; Ryter and Choi, 2010). Apoptosis to necrosis transition in response of CSE is a dose dependent process for pulmonary epithelial cells (Beas-2b) (Slebos et al., 2007). Autophagy is another process which is important in fundamental homeostatic process. Autophagy has important role in overcoming exogenous pathways but cell death can be possible due to prolonged and excessive Autophagy. (Shintani and Klionsky, 2004; Chen et al., 2008; Hwang et al., 2010). Increased biochemical and morphological markers of Autophagy in lung tissue to human with COPD is found. Increased Autophagy level promotes epithelial cell deaths and act as key player of COPD pathogenesis. (Thorburn, 2008; Kim et al., 2008). Increased Endothelial and Epithelial cell death in COPD lungs is related to decreased Vascular Endothelial Growth Factor (VEGF) and VEGF receptor R2 protein (Kasahara et al., 2001). In lung fibrosis Cigarette smoke causes cellular senescence with up regulation of p53 and p16 pathway. Cigarette induced senescence causes abnormal wound healing that provides pathogenesis of COPD. (Nyunoya et al., 2006).

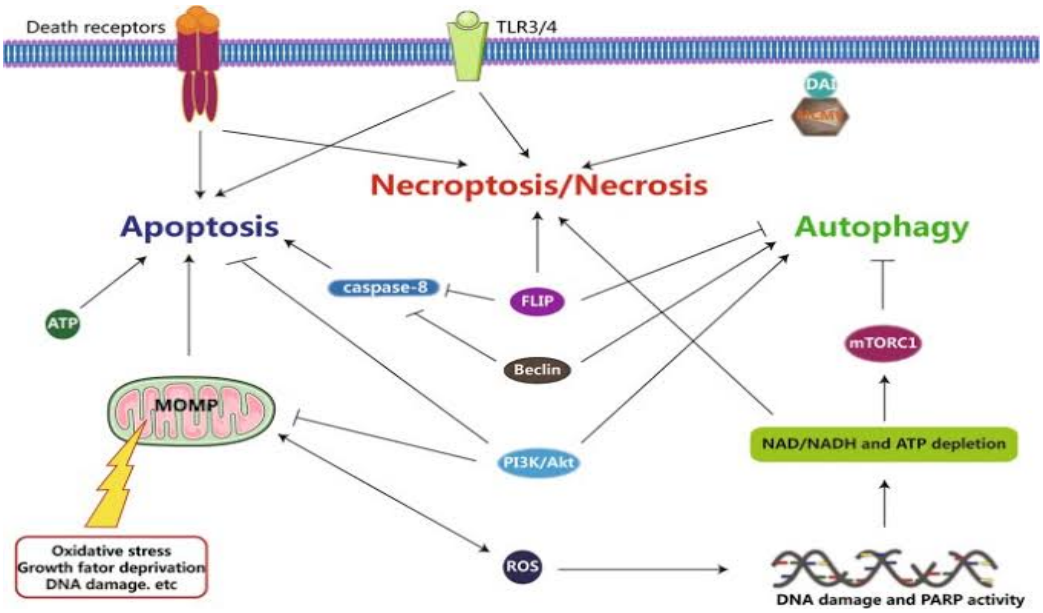

Figure 4. Relation between Autophagy, Apoptosis and Necrosis. (Chen, Q et al., 2018).

4. Cigarette smoke and associated diseases

Cigarette smoke causes various harmful diseases such as Asthma, COPD, Chronic Bronchitis, Lung Cancer, Emphysema etc. Oxidants found on cigarette causes oxidative stress on lungs, trachea, bronchi, nasal cavity etc.

Asthma

Asthma can be defined as breathing difficulties and trigger coughing due to airways narrow and swelling. It is one of the most terrible diseases. Smoking cause irritation in airways, deposition of mucus along with make airways swollen (Thompson et al., 2004). Common symptoms are wheezing, tightness in the chest, breathlessness, coughing, increased mucus production. (https://www.medicalnewstoday.com/articles/323523#what-is-asthma). Corticosteroid is one of the most effective drugs in asthma. Unfortunately in case of smoker, inhaled corticosteroid with short and middle-term effect not work with that much efficiency. (Thompson et al., 2004).

COPD

Chronic Obstructive Pulmonary Disease is a condition in which mucus layers of airways thickened and abnormal enlargement of alveoli, inactivation of antiprotease and redox-sensitive transcription deactivation mediated lung inflammation. Cigarette smoke is main culprit for it (Bartal, 2005). Symptoms of chronic obstructive pulmonary disease include Cough, chest discomforts, shortness of breath, and wheezing. Progressive or more serious symptoms may include respiratory distress, tachypnea, cyanosis, use of accessory respiratory muscles peripheral edema, hyperinflation, chronic wheezing, abnormal lung sounds. Several systematic disorders like skeletal muscle dysfunction and weight loss is associated with COPD (MacNee, 2005). wheezing, abnormal lung sounds. (https://www.medicinenet.com/copd_chronic obstructive_pulmonary_disease/article.htm). Several systematic consequences like skeletal muscle dysfunction and weight loss is associated with COPD (MacNee, 2005).

Chronic Bronchitis

Smoking causes Chronic Bronchitis (Mitchell,1964), It is caused by irritation to the respiratory epithelium of the bronchi, resulting in chronic inflammation, thickened fibroid bronchial walls with luminal narrowing; two main symptoms are excessive mucus production and chronic inflammatory cell infiltration of the bronchial wall (https://www.physio-pedia.com/Chronic _Bronchitis).

Emphysema

It is a pathological condition in which abnormal but permanent enlargement of air spaces distal to the terminal bronchiole occurs. Emphysema doesn't have any cure but omitting smoking can reduce lung damage. Symptoms of emphysema are tightness in the chest. Chronic cough that produces mucus, wheezing and a whistling or squeaky sound when breathing, shortness of breath, or dyspnea (https:// www.medicalnewstoday.com/articles/8934#definition).

Lung Cancer

Lung cancer is one of most popular cancer. Lung cancer is of two types -Non-small cell lung cancer, Small cell lung cancer. Cigarette smoke causes lung cancer (Hecht, 1999).Symptoms of lung cancer are frequent chest infections, such as bronchitis or pneumonia, a lingering cough that

may start to get worse, changes to a person's voice, such as hoarseness, shortness of breath and wheezing.
(https://www.medicalnewstoday.com/articles/323701#treatment).

Conclusion

Smoking is one of the leading causes of chronic obstructive pulmonary disease (COPD) and a trigger for COPD flare-ups. Smoking not only damages the air sacs, airways, and the lining of the lungs but also induces to failure of the lungs in breathing. Although there are several management therapies available for COPD management, but the cellular damages due to smoking are permanent and irreparable and results in disease exaggeration and suffering.

Conflict of interest

Authors declare that there is no conflict of interest.

References

Bartal, M. (2005). COPD and tobacco smoke. *Monaldi. Arch. Chest. Dis*. 63(4): 213-225.

Beutler, B. (1990). The complex regulation and biology of TNF (cachectin). *Crit Rev Oncog*. 2(1): 9-18.

Chang, W. H., Thai, P. , Xu, J. , Yang, D. C. , Wu, R. and Chen, C. H. (2017). Cigarette Smoke Regulates the Competitive Interactions between NRF2 and BACH1 for Heme Oxygenase-1 Induction. *Int. J. Mol. Sci.* 18(11): 2386.

Chen, Q., Kang, J. and Fu, C. (2018). The independence of and associations among apoptosis, autophagy, and necrosis. *Sig. Transduct. Target. Ther.* 3: 18.

Chen, Y., McMillan-Ward, E., Kong, J., Israels, S. J. and Gibson, S. B. (2008). Oxidative stress induces autophagic cell death independent of apoptosis in transformed and cancer cells. *Cell Death Differ.* 15: 171-182.

Chen, Z. H., Kim, H. P., Sciurba, F. C., Lee, S. J., Feghali-Bostwick, C., Stolz, D. B., Dhir, R., Landreneau, R. J., Schuchert, M. J., Yousem, S. A., Nakahira, K., Pilewski, J. M., Lee, J. S., Zhang, Y., Ryter, S. W. and Choi, A. M. (2008). Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. *PLoS One.* 3: e3316.

Church, D. F. and Pryor, W. A. (1985). Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ. Health. Perspect.* 64: 111-126.

Cullinan, S. B. and Diehl, J. A. (2006). Coordination of ER and oxidative stress signaling: the PERK/Nrf2 signaling pathway. *Int J Biochem Cell Bio*l. 38(3): 317-332.

Dalbey, W. E., Nettesheim, P., Griesemer, R., Caton, J.E. and Guerin, M. R. (1980). Chronic inhalation of cigarette smoke by F344 rats. *J. Natl. Cancer Inst*. 64: 383-390.

Ferson, M., Edwards, A., Lind, A., Milton, G. W. and Hersey, P. (1979). Low natural killer-cellactivity and immunoglobulin levels associated with smoking in human subjects. *Int. J. Cance*r. 23: 603-609.

Hecht, S. S. (1999). Tobacco Smoke Carcinogens and Lung Cancer, JNCI: *J. Natl. Cancer Inst.* 91 (14): 1194–1210.

Henson, P. M. and Tuder, R. M. (2008). Apoptosis in the lung: induction, clearance and detection. *Am J. Physiol. Lung Cell Mol. Physiol.* 294(4): L601-11.

Hwang, J. W., Chung, S., Sundar, I. K., Yao, H., Arunachalam, G., McBurney, M. W. and Rahman, I. (2010). Cigarette smoke-

induced autophagy is regulated by SIRT1-PARP-1-dependentmechanism: implication in pathogenesis of COPD. *Arch. Biochem. Biophys.* 500: 203-209.

Kasahara, Y., Tuder, R. M,, Cool, C, D,, Lynch, D, A,, Flores, S. C, and Voelkel, N. F. (2001). Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. *Am. J. Respir. Crit. Care Med.* 163: 737–744.

Kelsen, S. G., Duan, X., Ji, R., Perez, O., Liu, C. and Merali, S. (2008). Cigarette smoke induces an unfolded protein response in the human lung: a proteomic approach. *Am. J. Respir. Cell Mol. Biol*. 38: 541–550.

Kim, H. P., Wang, X., Chen, Z. H., Lee, S. J., Huang, M. H., Wang, Y., Ryter, S. W. and Choi, A. M. (2008). Autophagic proteins regulate cigarette smoke-induced apoptosis: protective role of heme oxygenase-1. *Autophagy.* 4: 887-895.

Kishimoto, T. (1989). The biology of interleukin-6. *Blood.* 74: 1-10.

Leigh, N. J., Palumbo, M. N. and Marino, A. M. (2018). Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tobacco Control.* 27: s37-s38.

MacNee, W. (2005). Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. *Proc. Am. Thorac Soc.* 2(1): 50-60.

Masdottir, B., Jónsson, T., Manfredsdottir, V., Víkingsson, A., Brekkan, A. and Valdimarsson, H. (2000). Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. *Rheumatol. (Oxford*) 39: 1202-1205.

Mathews, J. D., Whittingham, S., Hooper, B. M., Mackay, I. R. and Stenhouse, N. S. (1973). Association of autoantibodies with smoking, cardiovascular morbidity, and death in the Busselton population. *Lancet.* 2: 754-758.

Mishra, A., Chaturvedi, P., Datta, S., Sinukumar, S., Joshi, P., Garg, A. (2005). Harmful effects of nicotine. *Indian J. Med. Paediatr. Oncol*. 36(1): 24-31.

Mitchell, R. S., Vincent, T. N. and Filley, G. F. (1964). Cigarette Smoking, Chronic Bronchitis, and Emphysema. *JAMA*. 188(1): 12–16.

Nyunoya, T., Monick, M. M., Klingelhutz, A., Yarovinsky, T. O., Cagley, J. R. and Hunninghake, G. W. (2006). Cigarette smoke induces cellular senescence. *Am. J. Respir. Cell Mol. Biol.* 35(6): 681-688.

Petrache, I., Natarajan, V., Zhen, L., Medler, T . R., Richter, A. T., Cho, C., Hubbard, W. C., Berdyshev, E. V. and Tuder, R. M. (2005). Ceramide upregulation causes pulmonary cell apoptosis and emphysema-like disease in mice. *Nat. Med.* 11: 491-498.

Qiu. F,, Liang, C. L., Liu, H., Zeng, Y. Q., Hou, S., Huang, S., Lai, X. and Dai, Z. (2017). Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? *Oncotarget*. 8(1): 268-284.

Rahman, I. and MacNee, W. (1996) Oxidant/antioxidant imbalance in smokers and chronic obstructive pulmonary disease. *Thorax.* 51: 348-350.

Reynolds, H. Y. (1987) Bronchoalveolar lavage. *Am. Rev. Respir. Dis.* 135: 250-263.

Rutgers, S. R., Timens, W., Kauffman, H. F. and Postma, D. S.. (2001). Markers of active airway inflammation and remodelling in chronic obstructive pulmonary disease. *Clin Exp Allergy*. 31(2): 193-205.

Ryter, S. W. and Choi, A. M. (2010).

Autophagy in the lung. *Proc. Am. Thorac. Soc.* 7: 13-21.

Saha, S. P., Bhalla, D. K., Whayne, T. F. Jr. and Gairola, C. (2007). Cigarette smoke and adverse health effects: An overview of research trends and future needs. *Int. J. Angiol*. 16(3): 77-83.

Shintani, T. and Klionsky, D. J. (2004) Autophagy in health and disease: a double-edgedsword. *Science.* 306: 990-995.

Slebos, D. J., Ryter, S. W., van der Toorn, M. Liu, F., Guo, F., Baty, C. J., Karlsson, J. M., Watkins, S. C., Kim, H. P., Wang, X., Lee, J. S., Postma, D. S., Kauffman, H. F. and Choi, A. M. K. (2007). Mitochondrial localization and function of heme oxygenase-1 in cigarette smoke-induced cell death. *Am. J. Respir. Cell Mol. Biol*. 36(4): 409-417.

Sopori, M. (2002) Effects of cigarette smoke on the immune system. *Nat. Rev. Immunol*. 2: 372-377.

Stepanov, I. and Hecht, S. S. (2005). Tobacco-Specific Nitrosamines and Their Pyridine-N-glucuronides in the Urine of Smokers and Smokeless Tobacco *Cancer Epidemiol. Biomarkers Prev.* 14(4): 885-891.

Takeuchi, M., Nagai, S., Nakajima, A., Shinya, M., Tsukano, C., Asada, H., Yoshikawa, K., Yoshimura, M. and Izumi, T. (2001). Inhibition of lung natural killer cell activity by smoking: the role of alveolar macrophages. *Respiration.* 68: 262–267.

Thomson, N. C., Chaudhuri, R. and Livingston, E. (2004). Asthma and cigarette smoking. *Eur. Resp. J*. 24 (5): 822-833.

Thorburn, A. (2008). Apoptosis and autophagy: regulatory connections between two supposedly different processes. *Apoptosis.* 13(1): 1-9.

Touyz, R. M., Rios, F. J., Alves-Lopes, R., Neves, K. B., Camargo, L. L. and Montezano, A. C. (2020). Oxidative Stress: A Unifying Paradigm in Hypertension. *Can. J. Cardiol*. 36(5): 659–670.

Tuder, R. M., Petrache, I., Elias, J. A., Voelkel, N. F. and Henson, P. M. (2003). Apoptosis andemphysema: the missing link. *Am. J. Respir. Cell. Mol. Biol.* 28: 551-554.

Yoshida, T. and Tuder, R. M. (2007). Pathobiology of cigarette smoke-induced chronic obstructive pulmonary disease. *Physiol. Rev*. 87(3): 1047-1082.

Websites:

- https://www.medicalnewstoday.com/articles/323523#what-is-asthma
- https://www.medicalnewstoday.com/articles/323701#treatment
- https://www.medicalnewstoday.com/articles/8934#definition
- https://www.medicinenet.com/copd_chronic_obstructive_pulmonary_disease/article.htm
- https://www.physio-pedia.com/Chronic_Bronchitis