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Pharmaceutical Sciences **Review Article……!!!**

A CRITICAL REVIEW ON ETIOLOGY, MOLECULAR TARGETS AND CHEMICAL CARCINOGENS OF LUNG CANCER

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ABSTRACT

Lung cancer is still the leading cause of cancer death worldwide. Both histologically and molecularly lung cancer is heterogeneous. In most cases, activation of oncogenes and/or deactivation of tumor suppressor genes lead to uncontrolled cell cycle progression and inactivation of apoptotic mechanisms. It describes the major pathways and molecular alterations implicated in the development and progression of non-small cell lung cancer (adenocarcinoma and squamous cancer), and of small cell carcinoma. However, the genetic alterations often affect a common group of oncogenic signalling pathways. From this review we may come to know about the causes, symptoms, biology, molecular targets and chemical carcinogenesis of lung cancer. Thus, by adopting epigenetic alteration as a new hallmark of cancer is a logical and necessary step that will further encourage the development of novel epigenetic biomarkers and therapeutics.

1. INTRODUCTION:

Cancer can be defined as a disease in which group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. Normal cells are constantly subject to signals that dictate whether cells should divide, differentiate into another cell or die[1].

Lung cancer characterized by uncontrolled cell growth in tissues of the lung. If left untreated, this growth can spread beyond the lung by the process of metastasis into nearby tissue or other parts of the body.[2]

Based on histological, biological behavior, prevalence, prognosis and response to therapy the major subtypes of this category are Non-small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC).

In recent years, the incidence and mortality of lung cancer have shown a sharp rise in the world. Lung cancer is the most common cause of cancer death worldwide, with 1.38 million people dying every year, accounting for 18.2% of the total cancer deaths[3]. It is also the cancer with the highest morbidity and mortality in China, approximately 781,000 new cases and 626,000 deaths had been reported in 2014[4].

Based on the data from the Global cancer statistics 2018, it shows that among the males, incidence rate of the NSCLC is 223.0 per 100,000 and mortality rate is 166.6 per 100,000. Besides, in the female, the incidence rate is 182.6 per 100,000[5].

2. ETIOLOGY

2.1. Smoking

Main contributor of lung cancer is smoking especially cigarette smoking[6].Cigarette smoke contains 60 known carcinogens[7] which includes radioisotopes from the radon decay sequence, nitrosamine and benzopyrene. In which, nicotine appears to depress the immune response to cancerous growths in exposed tissue[8]. Across the developed world, 90% of lung cancer deaths in men during the year 2000 were attributed to smoking (70% for women). Smoking accounts for 80–90% of lung cancer cases[9].Passive smoking: the inhalation of smoke from another's smoking is a cause of lung cancer in nonsmokers. Studies from the US, Europe, the UK, and Australia have consistently shown a significantly increased risk among those exposed to passive smoke[10].Passive smoking causes about 3,400 deaths from lung cancer each year in the USA[11].

2.2. Radon gas

Radon is a colorless and odorless gas generated by the breakdown of radioactive radium, which in turn is the decay product of uranium, found in the Earth's crust. The radiation decay products ionize genetic material, causing mutations that sometimes turn cancerous. Radon is the second-most common cause of lung cancer in the USA[12].The risk increases 8–16% for every 100 Bq/m³ increase in the radon concentration[13].

2.3. Asbestos

Asbestos can cause a variety of lung diseases, including lung cancer. Tobacco smoking and asbestos have a synergistic effect on the formation of lung cancer[14].Asbestos can also cause cancer of the pleura, called mesothelioma (which is different from lung cancer) [15] Air pollution and heredity are the other factors of lung cancer.

2.4. Chemical Carcinogens

Carcinogens are a group of naturally occurring synthetic compound which are stable in the environment and require metabolic activation usually within the target cell to cause mutagenic and carcinogenic effect. About 81% of cancer result from exposure to naturally occurring man made environmental carcinogens. The hydrocarbons are widely distributed organic matter in the environment and also represent a very large group of carcinogens.[16,17]

2.5. Alcohol

A high intake of alcoholic beverages appears to raise the risk of developing lung cancer. For men, heavy consumption of beer and hard liquor has been associated with an elevated risk of lung cancer**[18]**.

2.6. Genetic Factor

Genetics factor play an important role in Lung Cancer. There is a region on the long arm of chromosome six has found to carry a gene associated with increased susceptibility for development of Lung Cancer.

2.7. Lung Disease

Several nonmalignant lung diseases have been identified as possible risk factors for developing lung cancer. These include chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), pneumoconiosis and tuberculosis. Lung cancer tends to develop in areas of the lung that are scarred from tuberculosis. It has been suggested that the increased risk for lung cancer with some of these conditions may be due to impaired clearance of carcinogenic substances and chronic inflammation with injury to bronchial epithelium.

2.8. Household Fumes

Exposure to household fumes groups the inhalation of cooking oil vapors and the particles emitted by domestic use of coal for cooking and heating. This type of exposure has been studied particularly in China, where traditional cooking practices use highly heated oils often in a poorly or unventilated kitchen.In particular, the smoke from these oils contains known carcinogenic PAHs and aldehydes[19]

2.9. Occupational exposures

Occupational exposures play a significant role in lung cancer etiology, and the risk of lung cancer is increased among workers employed in a number of industries and occupations. Two studies have reported an estimate of the proportion of lung cancer cases attributable to occupational agents in the UK to be 14.5%

overall and 12.5% in men in France. The most important occupational lung carcinogens are reported to be asbestos, silica, radon, heavy metals and polycyclic aromatic hydrocarbons [20]

3. SYMPTOMS [21,22]

Respiratory symptoms:

Coughing

Coughing up blood

Wheezing or shortness of breath

Systemic symptoms:

Weight loss

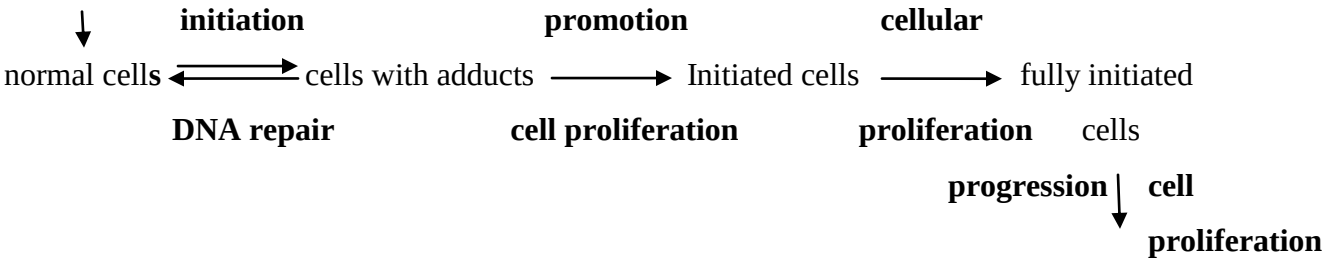
Fever

Clubbing of the fingernails

Fatigue chest pain, bone pain

4. MECHANISMS OF PRIMARY CANCER DEVELOPMENT

Chemical carcinogenesis usually undergoes three-steps, namely initiation, promotion and progression (*Flowchart 1*). The plausible cellular and molecular mechanisms involve interactions or covalent binding of carcinogens with intracellular DNA, RNA and proteins, resulting in gene-mutational alterations.[23,24]



Flowchart 1: Chemical carcinogenesis stages and occurrences involved in each one

5. TUMOR INITIATION, PROMOTION AND PROGRESSION

Initiation is the first step in cancer development. Initiators are the chemicals that are often not reactive with DNA, but altered by drug-metabolizing enzymes in the body and are then able to cause changes in DNA (mutations) often after a covalent binding.[7] Many initiators are specific to particular species or tissue types. Initiation is irreversible, i.e., once a particular cell has been affected by an initiator it is susceptible to promotion. Since initiation causes permanent genetic change, any daughter cells from the division of the mutated cell will also carry the mutation. There is a linear relationship between the dose of initiator and the quantity of produced tumor cells, i.e., the more exposure the higher risk of carcinogenesis.

Promotion is the second step that occurs on those cells already mutated by an initiator[10]. The promoters refer to the compounds that promote the proliferation of the cell into a large number of daughter cells containing the mutation created by the initiator. Promoters take effect only when the organism has been previously exposed to an initiator. Unlike initiators, promoters do not covalently bind to macromolecules or DNA within the cell, but many bind to receptors on the cell surface to affect intra-cellular pathways that increase cell proliferation[25].Two categories of promoters exist: specific promoters that interact with receptors on or in target cells and nonspecific promoters that alter gene expression without involving a known receptor. Tumor growth thus promoted is dose-dependent with a threshold and a maximum effect of promoters, i.e., very low doses will not promote tumor development and extremely high doses will not produce more risk. Promoters do not necessarily cause cancer on their own, but increase the clonal expansion of initiated cells, and ultimately leads to malignancy[11].

The third step progression refers to the serial transformations from a benign tumor to a neoplasm and to malignancy. Progression is associated with karyotypic changes since most advanced tumors show aneuploidy with the wrong number of chromosomes. This karyotypic change is coupled with an increased growth rate, invasiveness, metastasis and alterations in biochemistry and morphology due to the continuing mutations or genetic instability[26].Once this step is triggered, progression is irreversible.

In the practical animal models of malignancy, a two-stage carcinogenesis strategy is frequently employed to shorten the cancer development period by treating animals with an organ-specific cancer initiator followed by a promoter[27].

6. LUNG CANCER BIOLOGY

Cancer arises due to the mutation of genes leading to various hallmarks of cancer including: self sufficiency of growth signals, insensitivity to anti-growth signalling, apoptosis evasion, limitless replicative ability, angiogenesis control, invasion and metastasis.These carcinogenesis-driving mutations generally occur in either oncogenes or tumour suppressor genes (TSGs)

7. MOLECULAR TARGETS IN LUNG CANCER

Lung cancers that are related and unrelated to smoking (such as SCLC and NSCLC adenocarcinoma respectively) have very different somatic molecular profiles as exemplified by the difference in the mutational status of a number of key genes i.e. *p53*, *KRAS*, *EGFR* and erythroblastic leukemia viral oncogene homolog 2 (*ERBB2*, also known as *HER2*).

There are different mechanisms by which these genetic and cellular changes occur. The canonical mechanisms are mutation, chromosomal translocation or deletion, and dysregulated expression or activity of signaling pathways. These events may activate genes that promote dysregulated cell cycling and/or inactivate apoptotic pathways.

There are several pathways and molecular target involving in the development of lung cancer they are Receptor tyrosine kinases (RTKS), RAS pathway, BRAF/MAPK pathway, PI3K pathway, LKB1 (STK11)/AMPK pathway, TP53 pathway, RB1 pathway, MYC pathway, Epigenetic pathways, Oxidative stress, Developmental pathways, Other recurrent alterations.

Table 1: pathways and gene involved in lung cancer

Pathway	**AC**	**SQCC**	**SCLC**
	Gene involved	**Gene involved**	**Gene involved**
RTK	EGFR,ALK, MET, ERBB2,ROS,RET	EGFR,FGFR1-3, ERBB2, ERBB3,DDR2	FGFR1
RAS/RAF	KRAS,NF1,BRAF, NRAS	NF1,KRAS,HRAS,NRAS, RASA1,BRAF	
PI3K/AKT	PIK3CA,PTEN,AKT1	PIK3CA,PTEN,AKT1,AKT2, AKT3,TSC1-2	PTEN
LKB1/AMPK	LKB1		
TP53	P53,MDM2	TP53	TP53
RB1/CDKNA 2	CDKNA2	CDKNA2,RB1	RB1,CCNE1
MYC	MYC		MYC,MYCN,MYC L
Epigenetic regulation	SMARCA4,ARID1A, SETD2	MLL2	EP300,CREBBP, MLL
Developmental pathway	NKX2.1/TTF1	SOX2,TP63,NOTCH1,NOTC H2,ASCL4,FOXP1	SLIT2,EPHA7
Oxidative stress response	KEAP1	KEAP1,NRF2,CUL3	

8. CHEMICAL CARCINOGENESIS [27]

Carcinogenesis is a complex, multi-stage process involving the sequential mutation of growth control genes and the clonal expansion and progression of the resulting precancerous and cancerous cells to fully a malignant tumor. Chemicals may exhibit carcinogenic activity by affect any of the events leading to tumor formation.

Chemical carcinogens require activation to electrophiles to form covalent adduct with cellular macromolecules by microsomal enzymes (P450s). DNA is the cellular targets for activated chemical carcinogens and these mutations are keys to understand the mechanisms of carcinogenesis. Examples of genotoxicants include methyl methane sulfonate and N-nitroso dimethylamine.

Table 2: chemical carcinogens, mechanism, target organ and susceptible species

Classification	Compound	Abbreviation	Mechanism	Target organ	Susceptible species
N-nitroso compound (NOC)	N-Nitrosodiethylamine	DENA	Initiator	lung	Rat,mouse
	N-Methyl-No-nitro-N-nitrosoguanidine	MNNG	Complete carcinogen	Stomach	Rat, primate
	N-Nitrosodimethylamine	NDMA	Initiator Initiator	Liver Esophagus	Rat, mouse Rat
	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	NNK	Complete carcinogen + initiator	Lung	Mouse, rat
	N-Butyl-N-(4-hydroxy butyl)nitrosamine	BBN	Complete carcinogen	Bladder	Mouse, rat
Heterocyclic amine (HCA)	2-Amino-3,8-dimethylimidazo-[4,5-f]quinoxaline	MeIQx	Initiator	Liver	Rat
			Complete	Lung	Mouse

			carcinogen		
	2-Amino-3-methylimidazo[4,5-f]quinoline	IQ	Initiator	Liver	Rat, primate
Polycyclic aromatic hydrocarbon (PAH)	2-Acetylamino-fluorene	2-AAF	Promoter	Liver	Rat , mouse
	7,12-Dimethylbenzanthracene	DMBA	Complete carcinogen	Breast	Rat, mouse
			Initiator	Skin	Mouse
			Complete carcinogen	Oral cavity	Hamster
	Benzo[a]pyrene	BaP	Complete carcinogen	Lung	Mouse
			Complete carcinogen	Stomach	Mouse
			Complete carcinogen	Colon	Mouse
	3-Methylcholanthrene	MCA	Initiator	Lung	Mouse, rat
Food additive	Potassium bromate	KBrO3	Complete carcinogen	Kidney	Rat
Polychlorinated biphenyl (PCB)	2,3,7,8-Tetrachlorodibenzo-p-dioxin	TCDD	Promoter/initiator	Liver	Mouse, Rat
			Promoter	Lung	Mouse, Rat
Naturally occurring compound	Aflatoxin B1	AFB1	Complete carcinogen	Liver	Rat, mouse, fish,primate
	Asbestos	/	Complete	Lung,	Rat, mouse,

			carcinogen	pleura	hamster
	Aristolochic acid	AA	Complete carcinogen	Fore stomach	Rat , mouse
			Complete carcinogen	Kidney	Rat, mouse
Synthetic carcinogen	1,2-Dimethylhydrazine dihydrochloride	DMH	Complete carcinogen	Colorectrum	Rat, mouse
	Azoxymethane	AOM	Complete carcinogen	Colorectrum	Rat,mouse
	Methylazoxymethanol	MAM	Complete carcinogen	Colorectrum	Mouse
	4-Nitroquinoline 1-oxide	4NQO	Complete carcinogen	Oral cavity, esophagus	Rat, mouse
	Ethylnitrosourea	ENU	Complete carcinogen	Central nervous system	Rat
	N-Nitrosobis(2-hydroxypropyl)amine	BHP	Complete carcinogen	Lung	Rat
	Phenobarbital	PB	Promoter	Liver	Rat

9. CONCLUSION

This review has reported the causes, symptoms, biology, molecular targets and chemical carcinogenesis of lung cancer. Thus, by adopting epigenetic alteration as a new hallmark of cancer is a logical and necessary step that will further encourage the development of novel epigenetic biomarkers and therapeutics.

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