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APOPTOSIS IS A NEWER TARGET FOR LUNGS CANCER

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ABSTRACT

This review shows the targeted site for the prevention of cancer. In normal human, cell proliferation and cell destruction process is controlled by positive and negative regulation. In positive control, two families of proteins; cyclin and cyclin dependent kinases (cdks) have a major role. Each cdk is inactive until it binds to a cyclin, the binding enabling the cdk to phosphorylate the protein(s) necessary for a particular step in the cell cycle. In negative regulation, the mediators either stop the cell cycle or produce cell death (apoptosis). In, lung cancer and other cancer imbalance between positive and negative regulator take place. That means Activation of the positive regulator and inhibition of negative regulator may lead to different cancer. So the cell(s) under goes uncontrollable cell division and differentiation. Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality (1.35 million new cases per year and 1.18 million deaths), with the highest rates in Europe and North America. It is the second most commonly occurring form of cancer in most Western countries Mostly it is develop by inactivation of tumor suppressor genes. Damage to chromosomes 3p, 5q, 13q, and 17p are particularly common in small cell lung carcinoma. The *p53* tumor suppressor gene, located on chromosome 17p, is affected in 60-75% of cases also Mutations and amplification of EGFR are common in non-small cell lung cancer and inhibit the programmable cell death that means the apoptosis which play major roll in cell death. So these all are the main target for the anti cancer therapy.

Abbreviation: - CDKS (Cyclin Dependent Kinases), Cyl (Cyclin), epidermal growth factor receptor (EGFR).

Key Words: - Carcinoma, Bcl 2 family, Cell cycle, Cyclin Dependent Kinases, Cyclin.

INTRODUCTION

Lung cancer is a disease of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond

the lungs. The vast majority of primary lung cancers are **carcinomas of the lung**, derived from epithelial cells. Lung cancer, the most common cause of cancer-related death in men and also the most common in women, is responsible for 1.3 million deaths worldwide annually. [1] Lung cancer is the most commonly diagnosed malignancy in the world today. It has been the most common cancer in the world since 1985 and; by 2002 there were 1.35 million new cases, representing 12.4% of all new cancers. [2] It is also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the world total. Almost half (49.9%) of the cases occur in the developing countries — a big change since 1980, when it was estimated that 69% of the cases were in the developed countries. Worldwide, it is by far the most common cancer of men, with the highest rates observed in North America and Europe (especially Eastern Europe). With increasing prevalence of smoking, lung cancer has reached epidemic proportions in India. Chemotherapy applied as an adjunct to radiation improves survival and the quality of life to some extent but that is not very impressive.The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss.

The main types of lung cancer are *small cell lung carcinoma* and *non-small cell lung carcinoma*. This distinction is important, because the treatment varies; non-small cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation.[3]

Frequency of histological types of lung cancer

Histological type	Frequency (%)
Non-small cell lung carcinoma	80.4
Small cell lung carcinoma	16.8
Carcinoid	0.8
Sarcoma	0.1
Unspecified lung cancer	1.9

Sub-types of non-small cell lung cancer in smokers and never-smokers

Histological sub-type		Frequency of non-small cell lung cancers (%)	
		Smokers	Never-smokers
Squamous cell lung carcinoma		42	33
Adenocarcinoma	Adenocarcinoma (not otherwise specified)	39	35
	Bronchioloalveolar carcinoma	4	10
Carcinoid		7	16
Other		8	6

The most common cause of lung cancer is long-term exposure to tobacco smoke.[4] The occurrence of lung cancer in nonsmokers, who account for as many as 15% of cases,[5] is often attributed to a combination of genetic factors,[6,7] radon gas,[8] asbestos,[9] and air pollution,[10,11,12] including secondhand smoke.[13] Similar to many other cancers, lung cancer is initiated by activation of oncogenes or inactivation of tumor suppressor genes.[14] Oncogenes are genes that are believed to make people more susceptible to cancer. Proto-oncogenes are believed to turn into oncogenes when exposed to particular carcinogens. Mutations in the *K-ras* proto-oncogene are responsible for 10–30% of lung adenocarcinomas.[15,16] The epidermal growth factor receptor (EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion.[17] Mutations and amplification of EGFR are common in non-small cell lung cancer and provide the basis for treatment with EGFR-inhibitors. Her2/neu is affected less frequently.[17] Chromosomal damage can lead to loss of heterozygosity. This can cause inactivation of tumor suppressor genes. Damage to chromosomes 3p, 5q, 13q, and 17p are particularly common in small cell lung carcinoma. The *p53* tumor suppressor gene, located on chromosome 17p, is affected in 60-75% of cases.[18] Another protein is Rb protein which holds the cell cycle in Go phase during the phosphorylation form. Many of above gene included in to the apoptosis mechanism. It indicates that apoptosis have major role in to cell destruction or inhibition of their proliferation. So now a day apoptosis theory gives us newer therapeutic approach for to treat lung carcinoma.

Figure 1 show that, in normal human, cell proliferation and cell destruction process is controlled by positive and negative regulation. In positive control, two families of proteins; cyclin and cyclin dependent kinases (cdks) have a major role. Each cdk is inactive until it binds to a cyclin, the binding enabling the cdk to phosphorylate the protein(s) necessary for a particular step in the cell cycle. After the phosphorylation take place cyclin is degraded by ubiquitin/protease system. There are eight groups of cyclins. Those important in the control of the cell cycle are cyclins A, B, D and E. each cyclin is associated with and activates the particular cdk(s).[19] Cyclin A activates cdks 1 and 2; cyclin B, cdk 1; cyclin D, cdks 4 and 6; cyclin E, cdk 2. In negative regulation, the

mediators either stop the cell cycle or produce cell death (apoptosis). Different mediators are Rb protein that holds the cycle in Go phase while it is hypophosporylated.[20] Another two families inhibitors are, one is CIP family (cdk inhibitor proteins, also termed KIP or kinase inhibitory proteins) – p21, p27, and p57. Other is Ink family (inhibitor of kinase) – p16, p19 and p15. p 21 is the under control of the gene p51. Here the below figure shows the normal cell cycle include S (synthesis) phase, M (mitosis) phase, G1 (Check point 1 between M and S phase where cell is preparing for S phase by synthesis messenger RNAs and proteins need for DNA replication), G2 (check point 2 between S and M phase where double the number of chromosomes), Go is the quiescent phase where the cell is not constantly divide, here the Rb protein is hypophosporylated. If the DNA or cell is damaged the repairing of cell is take place either in check point 1 or check point 2. If the repair is fails then cell goes in to the apoptosis.[19]

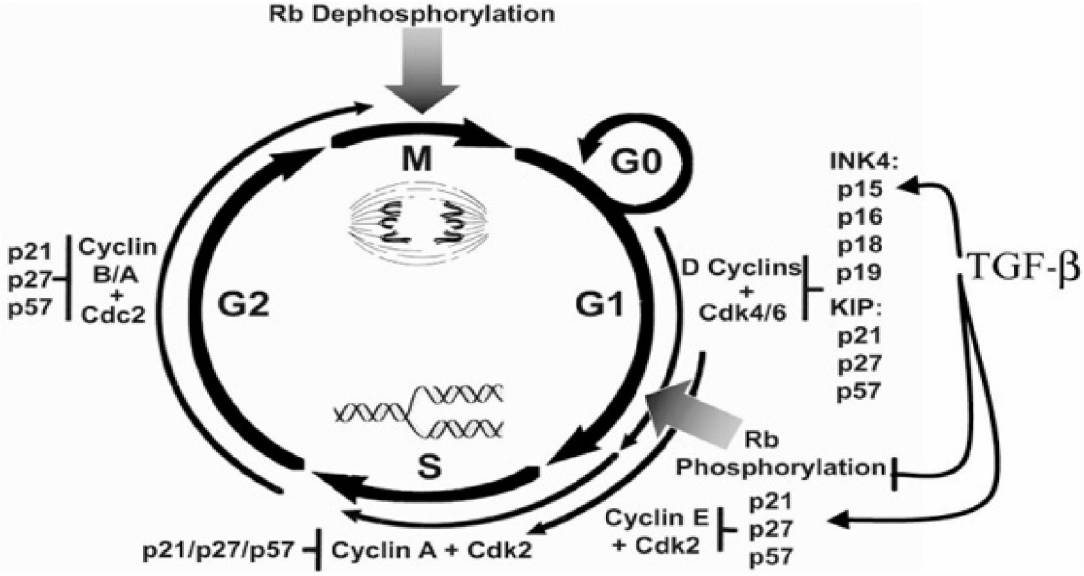

Figure 1

Genetically regulate positive and negative regulators. (Activation of Negative regulators and inhibition of positive regulators is main target for lung cancer drugs)

In, lung cancer and other cancer imbalance between positive and negative regulator take place. That means Activation of the positive regulator and inhibition of

negative regulator may lead to different cancer. So the cell(s) under goes uncontrollable cell division and differentiation, shown in figure 2.

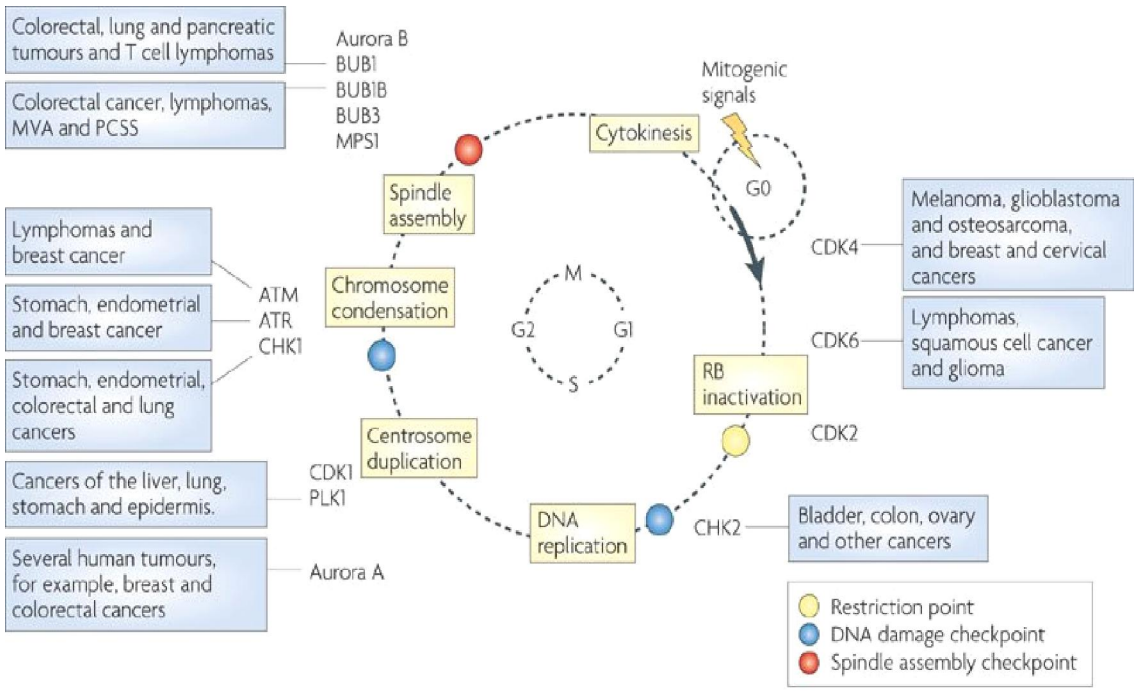

Figure 2

Activation of positive regulator and inhibition negative regulator

So it is essential to inhibit the positive regulator and activate the negative regulator by various anti cancer drugs for prevent the uncontrollable cell division and cell proliferation for prevent or development of the lung cancer. And for this, the knowledge of apoptosis is essential because apoptosis is "cell suicide by a built-in self destruct mechanism" consisting of a genetically programmed sequence of biochemical events. Now a day Apoptosis is the major newer target for many anti cancer therapy. Apoptosis of cell take place by two pathways; first one is Death receptor pathway where Lurking in the plasma membrane of most cell types are members of the tumour necrosis factor receptor (TNFR) superfamily, which function as death receptors. Each receptor has a 'death domain' in its cytoplasmic tail. Stimulation of the receptors by an external ligand such as tumour necrosis factor (TNF) itself or TRAIL[21] causes them to get together in three (trimerise), and recruit an adapter protein that complexes with the trimer by associating with the death domains. Then it activate the caspase 8 known as initiator caspase which activate the effector caspase 3 which poduce the cleavage and

inactivation of enzyme and structural constituents, fragmentation of genomic DNA etc and leads to apoptosis.[19]

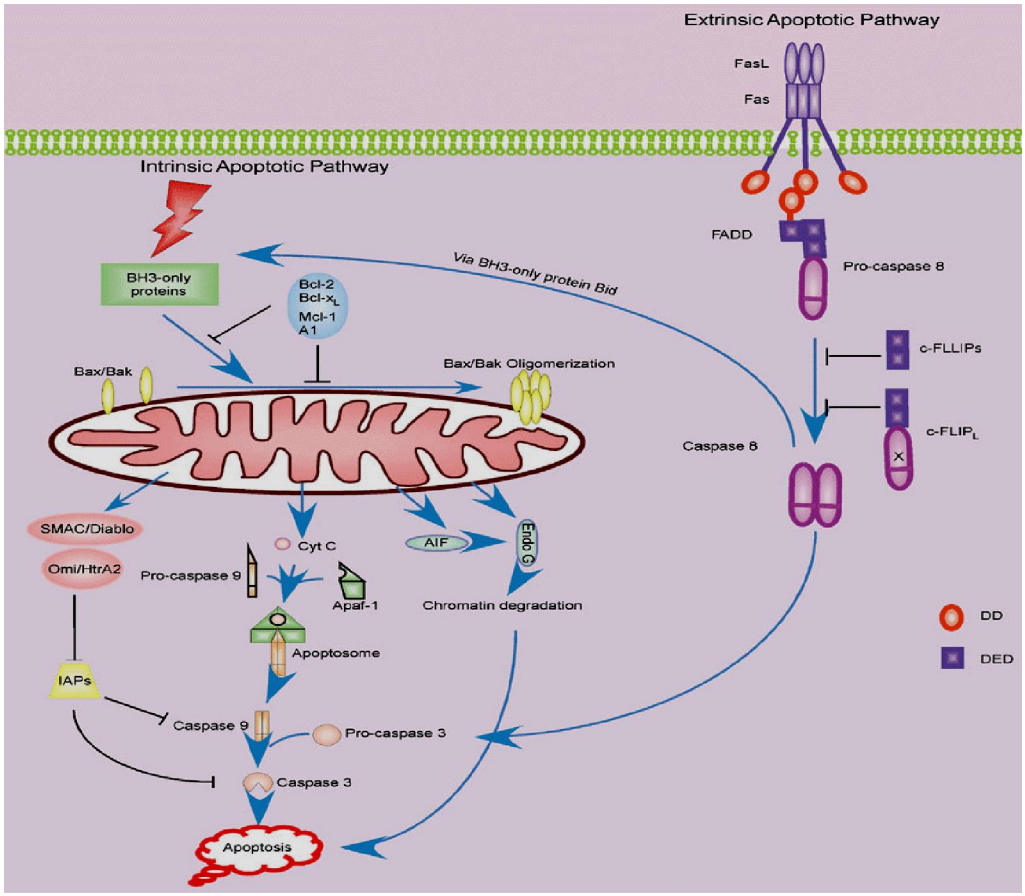

Figure 3

Extrinsic and intrinsic target for lung cancer drugs

Figure 3 shows the another pathway is the mitochondrial pathway, if the DNA damage and withdrawal of survival factor take place, cause activation of the p53 gene which has a control on p21 protein so p21 get activates and activate the pro-apoptotic Bh3 family (Bad, Bax, Bak) and produce the damage of mitochondrial cell wall damage which release cytochrom-c, it activate the APAf-1 (apoptotic protease activating factor-1) which activate the procaspase 9 and the combination of these three is known as apoptosome produce activation of caspase 9 and finally activate the effectors caspase 3 and follow the common pathway and leads to cell death or apoptosis.[22]

Now a day EGFR particular for lung cancer is the newer target because of, approximately 10% of patients with non-small cell lung cancer (NSCLC) have an abnormality involving Epidermal Growth Factor Receptor (EGFR) (Fig. 4). The presence

of an EGFR abnormality may have a significant effect on how your cancer responds to anti-EGFR therapy. In addition, as shown in the illustration, the molecular pathways by which EGFR abnormalities drive cancer development are extremely complex and involve many interconnected signaling pathways, including both signaling molecules (such as Ras and PI3K) and receptors (such as MET and HER-2).

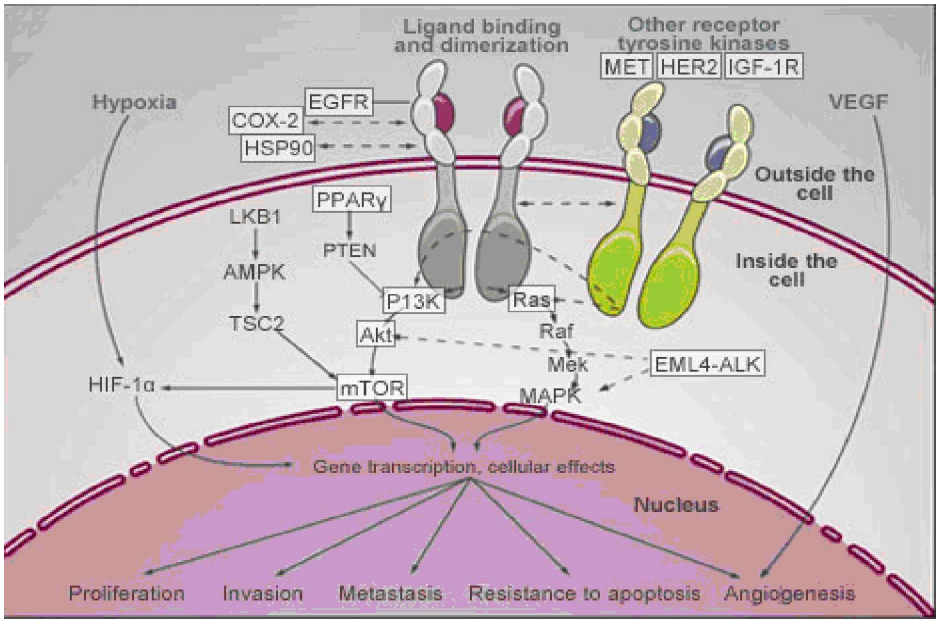

Figure: 4

Abnormalities in Epidermal Growth Factor Receptor (EGFR)

These above all theory give the general idea for the target of the drug(s) on lung cancer. So the newer target for drugs in lung cancer is as under,

1) Rb protein as newer target for lung cancer: If the Drug(s) maintain the Rb protein in their hypophosphorylation forms in Go stage produce inhibition of cell proliferation.
2) Cyclin and cdk(s) as newer target for lung cancer: when cyclin bind with the cdk leads to phosphorylation of various proteins and promote the cell proliferation and differentiation. So if any drug can bind with the cdk(s) instead of cyclin it deactivate the complex and inhibit the further process of cell proliferation.
3) The Bcl2 family as a newer target for lung cancer: - The Bcl2 family consist apoptotic (Bad, Bax, Bak) and antiapoptotic (Bcl-xl, Mcl-1). So here, activation of apoptotic and inhibition of antiapoptotic Bcl2 family produce the cell death.

4) P53 is newer target for lung cancer: if the drug(s) activate the gene p53 it causes activation of apoptic path and produce cell death.
5) Death receptor is newer target for lung cancer: Activation of death receptors can also leads to cell death or inhibit the cell proliferation.
6) Effectors caspase 3 is newer target for lung cancer: Caspase 3 is effectors caspase by which apoptic pathway follows the common pathway and produce the cell death.
7) EGFR is the newer target for lung cancer: Inhibit the activation of EGRF may produce suppression of molecular pathway by which cancer is develop.

DISCUSSION AND CONCLUSION

Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality (1.35 million new cases per year and 1.18 million deaths), with the highest rates in Europe and North America [23] It is the second most commonly occurring form of cancer in most Western countries, and it is the leading cancer-related cause of death. In contrast to the mortality rate in men, which began declining more than 20 years ago, women's lung cancer mortality rates have been rising for over the last decades, and are just recently beginning to stabilize. The evolution of "Big Tobacco" plays a significant role in the smoking culture. Not all cases of lung cancer are due to smoking, but the role of passive smoking is increasingly being recognized as a risk factor for lung cancer.[23] Reviewer suggests that apoptosis and the genes that control it have a profound effect on the malignant phenotype. For example, it is now clear that some oncogenic mutations disrupt apoptosis, leading to tumor initiation, progression or metastasis.[24]

As well as Recent studies identify the product of the p53 tumor-suppressor gene as an important regulator of apoptosis in tumor cells. At the same time, clinical studies implicate p53 mutations in pleiotropic resistance to cytotoxic cancer therapy. Together, these observations suggest that inactivation of p53 promotes resistance to anticancer agents by attenuating apoptosis. This view identifies p53 as a potential drug target and suggests several strategies for therapeutic intervention.[25] And the pathophysiology of lung cancer shows the major role of inactivation of tumor suppressor genes. Damage to chromosomes 3p, 5q, 13q, and 17p are particularly common in small cell lung carcinoma. The *p53* tumor suppressor gene, located on chromosome 17p, is affected in 60-75% of cases also Mutations and amplification of EGFR are common in non-small cell

lung cancer and inhibit the programmable cell death that means the apoptosis which play major roll in cell death. So these all are the main target for the anti cancer therapy.

Novel drugs are being developed which interact with the programmed cell death (apoptotic) machinery in cancer cells, thereby causing these cells to commit suicide and to be removed from the body. Research is also directed to investigate why the cancer cells sometimes lose the ability to undergo apoptosis after a certain period of time and methods are being developed to reactivate this cell death process. [26] So, here it is essential to activate negative regulated and suppress the positive regulator in cancer cell to prevent the cancer.

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