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Molecular understanding of lung cancers-A review

Chinnappan Ravinder Singh*, Kandasamy Kathiresan

Centre of Advanced Study in Marine Biology, Faculty of Marine Sciences, Annamalai University, Parangipettai-608 502, Tamil Nadu, India

PEER REVIEW

Peer reviewer

Dr. Vijayabaskar Pandian, Department of Radiation Oncology, The Oklahoma University Health Science Center, 940, Stanton L. Young Boulevard, Biomedical Sciences Building, Room No. 737, Oklahoma City-73104, OK, USA.
Tel: 405 6868443
E-mail: baski_bos@yahoo.co.in

Comments

This is the excellent review given by the author. This may help to understand the global problem lung cancer and to know the importance of chemotherapy; sofar 45 different mangrove plants have the anti-cancer potential but not studied thoroughly. This study clearly indicates the much more bottomless study need to find out the remedy for this problem and mangrove may be very good source. Also UGC, Government of India supported this brilliant study.
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ABSTRACT

Lung cancer is considered to be the most common cancer in the world. The purpose of this paper is to review scientific evidence, particularly epidemiologic evidence of overall lung cancer burden in the world. And molecular understanding of lung cancer at various levels by dominant and suppressor oncogenes.

KEYWORDS

Lung cancer, p53 mutation, Mangroves, Anti-cancer drugs.

1. Introduction

Lung cancer is considered as the most common cancer in the word[1]. Until today, several biological events have been identified in lung adenocarcinoma, including epidermal growth factor receptor mutations and anaplastic lymphoma kinase translocations, offering new hopes to patients with metastatic disease. Lung cancer remains a major global health problem accounting for more than a million (1.8 million) annual deaths worldwide[3,4], especially it kills more people than from colon, breast, and prostate cancers[5]. Lung cancer responsible for 17.8% of all cancer death[6]. In India, around 555 000 people died of cancer in 2010[7], according to estimates published in The Lancet today.

2. Carcinogens of lung cancer

2.1. Smoking and lung cancer

Lung cancer rates are largely determined by smoking patterns, medical, occupational and environmental radiation exposures have also been shown to increase risks of lung cancer[8]. The disease of lung cancer was not recognized as a disease until 1761[9], the first link between lung cancer and smoking was reported in 1929 by physician

*Corresponding author: Dr. Chinnappan Ravinder Singh, UGC Dr.D.S. Kothari Post Doctoral Fellow, Centre of Advanced Study in Marine Biology, Faculty of marine sciences, Annamalai University, Parangipettai- 608 502, Tamil Nadu, India
Tel.: 09597992543
Fax: 91-4144243555
E-mail: chinnaravinder@yahoo.co.in

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Fritz Lickint from Germany. It is believed that smoking is the primary etiologic agent in more than 80% of lung cancer patients[10]. Cigarette smoking is also an important cause of esophageal, oral, oropharyngeal, hypopharyngeal and laryngeal cancers as well as pancreatic cancer, bladder cancer, and cancer of the renal pelvis including vascular diseases[11]. The mainstream smoke emerging from the mouth-piece of a cigarette is an aerosol containing about 1 010 particles/mL and 4 800 compounds include poly aromatic hydrocarbons[12]. It is experimentally proved that, cigarette contains PAH like aza-arenes, tobacco-specific nitrosamines, *e.g.* 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1,3-butadiene, ethyl carbamate, ethylene oxide, nickel, chromium, cadmium, polonium-210, arsenic, and hydrazine convincingly induce lung tumors[12]. Among the poly aromatic hydrocarbons, benzo[a]pyrene (BaP) is the most extensively studied compound against lung cancer through administration or inhalation[13]. Studies of non-smokers exposed to second hand smoke in their workplace show an increased risk of lung cancer[14].

2.2. Radiation and lung cancer

Lung cancer rates are also strongly associated with radiation, with an estimated excess relative risk per Gy of 0.81 and excess absolute risk of 7.5 per 10 000 person-year Gy[15].

2.3. Pollution and lung cancer

Pollution from transport also associated with the development of cancer, particularly lung cancer[16]. A recent report published in Europe related to relationship between lung cancer and vehicle-related pollution[17]. Exposure to NO_2 from heavy traffic roads increases the risk of lung cancer[18,19]. Reasons for believing that air pollution might be an important factor in the development of lung cancer were first, the presence in polluted air of known human carcinogens[20]. Benzopyrene in air is one of the important risk factor of lung cancer[21,22]. Use of unprocessed solid fuel for cooking most found in India causes indoor air pollution which may have the wide-range of chemicals is the important risk factor of lung cancer[23, 24].

2.4. Chemicals and lung cancer

Exposure to chemicals, whether naturally occurring or industrially produced, is a constant and inescapable fact of life. Natural chemicals such as arsenic, asbestos, chromium, nickel and vinyl chloride and to the natural radioactive gas radon increased the risk of lung cancer[25]. Genetic predisposition: especially polymorphisms of the tumor suppressor genes and the allelic variants of the genes involved in detoxification are implicated into the susceptibility to the disease. Chemical carcinogens has specific effect on metabolic pathways by interfering with the genetic integrity[26].

2.5. Radon and lung cancer

Radon is an invisible, odorless, and tasteless radioactive gas that occurs naturally in soil and rocks. Radon-222 is a naturally occurring gas that originates from the decay product of uranium-238, and in turn decays into short-lived radioactive alpha and beta emitting particles[27]. Exposure to radon (in mines or even houses) can cause damage to the lungs that may lead to lung cancer[28]. In 1988, radon was classified as a Class 1 human carcinogen and it is established that high levels of inhalation exposure can cause lung cancer[29]. Since radon is an inert gas, when it is inhaled, the gas is mostly exhaled except radon will decay to other radioactive decay products, such as polonium, bismuth and lead. These are solid fine radioactive particles that can be inhaled and subsequently reside in the lung. The link between radon and lung cancer dates back to early reports of underground miners in the 16th century who were anecdotally observed to have greater risk of respiratory related mortality, later determined to be lung cancer[30].

2.6. Asbestos and lung cancer

Asbestos (actinolite, amosite, anthophyllite, chrysotile and tremolite) is the name of a group of minerals that occur naturally as fibers and are used in certain industries. Asbestos is one of the most important occupational carcinogens causing about half of the deaths from occupational cancer. When the particles are inhaled, they can lodge in the lungs, damaging cells and increasing the risk for lung cancer[31].

2.7. Lung diseases and lung cancer

Certain lung diseases, such as tuberculosis, increase the risk of developing lung cancer. Lung cancer tends to develop in areas of the lung that are scarred from tuberculosis[32].

3. Symptoms of lung cancer

Lung cancer symptoms are not often felt until the disease has developed into an advanced stage. Constant chest pain, chronic cough, coughing up blood (hemoptysis), dyspnea (difficulty breathing), fatigue, lung infection (pneumonia, bronchitis), shortness of breath, swollen lymph nodes, loss of appetite and weight loss, and wheezing, bone pain and tenderness, breast development in men, weakness, chills, speech difficulties or changes (*i.e.*, hoarseness), droopy eyelids, swelling of the face and neck, fever, joint pain and swelling, muscle weakness, pale or bluish skin *etc*[33,34].

4. Apoptosis

Apoptosis is a genetically programmed process

of cell death required for maintaining homeostasis under physiological conditions and for responding to various internal and external stimuli. Cells committed to apoptosis are characterized by membrane blebbing, cytoplasmic shrinkage, nuclear chromatin condensation and DNA fragmentation. Cancer cells have developed novel mechanisms for evading chemotherapy-induced apoptosis[35].

5. Molecular biology of lung cancer

It has been broadly recognized that cancer is a disease caused by molecular alterations in either proto-oncogenes or tumor suppressor genes. In order to make an impact on lung cancer, we must understand the molecular abnormalities to target better therapeutics. Lung cancers exhibit multiple genetic lesions including mutations activating the dominant cellular proto-oncogenes as well as those inactivating the tumor suppressor genes. It is generally accepted that the pathogenesis of human cancer involves the accumulation of multiple molecular abnormalities over time. Those alterations lead to acquired cellular capabilities that can be classified in the following six functional sets: 1) self-sufficiency in growth signals due to mutations in proto-oncogenes, 2) insensitivity to anti-proliferative signals as a result of mutations affecting the tumour suppressor genes, 3) evading of apoptosis by up-regulation of anti-apoptotic or down-regulation of pro apoptotic molecules, 4) limitless replicative potential due to the activation of telomerase, 5) sustained angiogenesis and 6) capability for tissue invasion and capability for dissemination into distant sites (metastasis)[36].

5.1. Dominant and suppressor genes in lung cancer

Lung cancer has majorly divided into small cell (small round cells in the lung) lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (cells grow inside the lung other than the small cells). In 2011 NSCLC remains the principal cause of cancer-related death worldwide[37,38], accounting for more than one million deaths per year. These lung cancer cell can travel and spread to the other organs called as secondary cancer[39]. There are different oncogenes expressions have been investigated in NSCLC and SCLC. There are two forms of oncogenes: dominant oncogenes, exert their effect by overtaking the normal cellular growth function and tumor-suppressor genes, that exert their effect in controlling cellular growth[40].

5.2. Dominant oncogenes

RAS genes (dominant) most frequently altered gene, with mutations occurring in 17%-25% of all cancers, 35% of lung cancers[41], which involve in the signal transduction and cell proliferation, which consist of K-RAS, H-RAS, and N-RAS. K-RAS was initially identified in a human lung cancer cell in 1982[42], and since then has been shown to be mutated in 35%-50% of all NSCLCs. RAS proteins are activated when it bind to guanosine triphophate (GTP) and inactivated by GTPase -activating protein (GAP) by hydrolyzing GTP to guanosine diphosphate (GDP). Mutations at or near the GTP-binding domain of RAS protein prevents the inactivation of GTP, thereby resulting in continuous RAS activity. Also GAP proteins have the transforming potential and responsible for point mutation at the codon 12 and 13 in the encoding gene[43]. Unfortunately, in approximately 50% of adenocarcinoma and for those harbouring K-RAS mutations, the most frequent mutation in Caucasian lung adenocarcinoma, so far no specific drug demonstrated efficacy.

5.3. MYC genes

Activation of this MYC (dominant) (c-MYC and N-MYC, and L-MYC) in lung cancer is gene amplification with resulting over-expression[44]. It is now well-established that the deregulated expression of c-myc plays a significant role in human cancer development. The c-Myc protein or the c-*myc* gene is overexpressed in a wide variety of human cancers. The universal deregulation of c-*myc* *N-myc* genes expression in tumor cells suggests that this oncogene represents an attractive target for cancer therapeutic purposes[45]. c-*myc* is expressed at elevated levels in most tumors[46]. In addition, several tumors contain genetic alterations (*i.e.*, translocations, gene amplifications and mutations in regulators of *c-myc* expression), which directly affect c-*myc* expression. Unlike c- and N-*myc*, the evidence for a causal involvement of L-*myc* activation in human cancers is limited. In SCLC the frequency of L-*myc* amplification is rather low (~10%), and c- as well as N-*myc* amplifications also occur in SCLC. Mutational inactivation of the MYC antagonist Mxi-1 in prostate carcinoma may be another mechanism of MYC activation[47].

5.4. HER-2/NEU genes

HER-2/NEU gene (proto-oncogene) is a growth factor receptor, over expression of these genes associated with an adverse prognosis in adenocarcinoma of the lung[48], and 4.BCL-2 (proto-oncogene) inhibit the programmed cell death/apoptosis, overexpressing cells have expansion of cell populations secondary to lack of apoptosis[49].

5.5. Tumor suppressor genes

Tumor suppressor genes include those on chromosomes ip, lq, 3pl4, 3p2l.3, 3p25 (VHL gene), 5q21 (APCIMCC gene cluster), 9p21-Z2 (interferon gene cluster), lip, 13q (rb gene), i6p24, and i7p (p53 gene). In lung cancer chromosomal abnormalities (including loss of complete chromosomes or portions thereof) occur. In NSCLC, chromosomal aberrations have been described on 3p, 8p, 9p, 11p, 15p, and 17p with deletions of chromosomes 7, 11, 13, or 19. Also, in SCLC,

chromosomal abnormalities have been described on 1p, 3p, 5q, 6q, 8q, 13q, or 17p[50]. Chromosomal abnormalities in lung cancer have been the loss of the short arm of chromosome 3p[51]. The loss of alleles at 3p is observed in >90% of SCLC tumors and approx 50% of NSCLC tumors[52].

5.6. p53 genes

Its family includes p53, p73, and p63. The gene p53 located in the chromosome 17p13.1 encodes a nuclear protein that acts as a transcription factor and blocks the progression of cells through the cell-cycle late in the G1 phase. p53 gene mutations (deletion, point mutation and overexpression) cause a loss of tumor-suppression function, promoting cellular proliferation. Lung cancer, type of point mutation is a GC to TA transversion. Some of the p53 proteins also have transforming potential which can bind with normal p53 and inactivate[53]. But in lung cancers, the p53 mutational patterns are different between G to T transversions and large fractions of the mutations are G to T events. The prevalence of G to T transversions is 30% in lung cancer but only 12% in normal and p53 mutations in lung cancers can be attributed to direct DNA damage[54]. Loss of the p53 tumor suppressor pathway contributes to the development of most human cancers. These p53 tumor suppressor genes are mutated in over two thirds of lung cancers[55]. When mutated, p53 can function as an oncogene and accumulate in the cytoplasm[56]. Mutated p53 exhibits a prolonged half-life and can thus be found to be overexpressed in about 50% of lung cancers by immunohistochemistry[57]. Mutations in p53 deactivate its transcriptional activity, while replacement of a wild-type p53 in lung cancer cells inhibits growth and tumorigenicity suggesting that p53 acts as a master growth regulatory switch[58-60]. Also the loss of heterozygosity involving several chromosome 3p regions accompanied by chromosome 3p deletions are detected in almost 100% of small (SCLCs) and more than 90% of non-small (NSCLCs) cell lung cancers which appear early in the pathogenesis of lung cancer[61].

Perhaps as many as 10 or 20 genetic mutations have occurred by the time lung cancer becomes clinically evident[62-64]. The p53 gene probably works in the nucleus in complex with other proteins to act as a transcription factor to turn on a whole panel of tumor suppressor or growth regulatory genes[65-68]. p53 specifically binds to a consensus DNA binding sequence, consisting of repeats of the 10 bp motif 5'-PuPuPuC(A/T)(T/A)GPyPyPy-3', located in the promoter or introns of its downstream target genes and thus transactivates the expression of these genes[69].

5.7. RB genes

RB gene is a 105 kDa phosphoprotein located on the chromosome13q14.11, important in regulating the cell cycle during G0/G1 phase. A deletion of the RB gene and the abnormal expression of the tumor-suppressor gene RB may be an adverse prognosticator in SCLC. Chemical carcinogens activate NF-κB (nuclear transcriptional factor) inflammation-associated pathways, stimulating the anti-apoptotic tumor inducing factors (STAT3) and pro-apoptotic tumor suppressor genes (ARF, p53)[70,71].

5.8. p16 and p15 Genes

Certain lung cancer cells have a characteristic deletion of chromosome 9p21, from this region the genes have identified p16[72]and p15 and other genes on chromosome 3p also responsible for lung cancer was identified[73].

6. Recent research on chemotherapy

Very few of the advances in chemotherapeutics have enhanced survival over the past decade. Treatment for cancer disease includes surgery, chemotherapy, radiation therapy or targeted drug therapy. Chemotherapy uses anti-cancer drugs which kill the cancer cells it can improve the chance of living longer. One or more chemotherapy drugs may be given through intravenously or orally. A combination of drugs usually is given in a series of treatments over a period of weeks or months, with breaks in between so that you can recover. Chemotherapy can be used as a first line treatment for lung cancer or as additional treatment after surgery. In some cases, chemotherapy can be used to lessen side effects of cancer disease.

Chemotherapy is an important treatment for SCLC[74]. Use of chemotherapy with cisplatin plus etoposide is reported effective when the tumor is localized within the field of irradiation (limited disease),while cisplatin plus etoposide with chemotherapy has been the standard treatment for a long time.

Several anticancer agents from tropical plants are in clinical use all over the world[75]. A recent trend in the chemotherapy for advanced lung cancer is the reports of efficacy of several regimens combining newly developed antineoplastic agents and platinum-based antineoplastic agents[76,77].

The marine flora are rich source of medicinally important compounds predominantly belonging to polyphenols and sulphated polysaccharides. The chemicals have displayed an array of pharmacological properties especially antioxidant, immunostimulatory, and antitumour activities. The phytochemicals possibly activate macrophages, induce apoptosis, and prevent oxidative damage of DNA, thereby controlling carcinogenesis[78]. Even the marine flora especially mangrove resources enriched with chemicals, it has ration of unexplored for anticancer lead compounds. Around 45 mangroves and associated species like *Acanthus illicifolius*, *Acanthus ebracteatus*, *Acrostichum aureum*, *Aegiceras corniculatum*, *Avicennia africana*, *A. nitida*, *Avicennia alba*, *Avicennia marina*, *Bruguiera exaristate*, *Bruguiera Sexangula*, *Barringtonia asiatica*, *Bruguiera cylindrica*, *Bruguiera gymnorrhiza*, *Buddleja parviflora*, *Bruguiera gymnorrhiza*, *Ceriops decandra*, *Ceriops tagal*,

Cissus carnosa, *Cordia cochinchinensis*, *Cynometra ramiflora*, *Calophyllum inophyllum*, *Derris trifoliata*, *Excoecaria agallocha*, *Flagellaria indica*, *Heritiera fomes*, *Ipomea pes-caprae*, *Lumnitzera racemosa*, *Nypa fruticans*, *Pandanus odoratissimu*, *Phoenix paludosa*, *Rhizophora mucronata*, *Rhizophora apiculata*, *Rhizophora stylosa*, *Sonneratia apetala*, *Sesuvium portulacastrum*, *Suaeda maritima*, *Sarcolobus globosus*, *Sonneratia alba*, *Sonneratia caseolaris*, *S. ovata*, *Stenochlaena palustris*, *Suaeda maritima*, *Trianthema decandra*, *Terminalia catappa*, *Xylocarpus granatum*, *Xylocarpus rumphii*, *Xylocarpus granatum*, and *Weddelia biflora* reported to have anti-cancer activity but very few studies only has been completed on lung cancer.

7. Conclusion

Peoples are majorly concentrating research on terrestrial plants for long period. In recent years peoples are attracted by the mangrove species due to its rich source of medicinal properties with lot of pharmaceutical application. But much attention needs to find out the remedy for this serious global problem with lung cancer.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Lung cancer remains a major global health problem accounting for more than a million (1.8 million) annual deaths worldwide especially it kills more people than from colon, breast, and prostate cancers. Finding remedy from the plant sources is an important to protect the human population.

Research frontiers

This is the study critically reviewed to understand the lung cancer in molecular level and the medicinal benefits of mangrove plants.

Related reports

This is the innovative idea to find out the remedy for lung cancer from the mangroves. Number of related research has published but they were concentrated the terrestrial plants. A recent trend in the chemotherapy for advanced lung cancer is the reports of efficacy of several regimens combining newly developed antineoplastic agents and platinum-based antineoplastic agents.

Innovations and breakthroughs

In this review, author pointed out number of innovative idea to find out the remedy for lung cancer. Also reviewed the lung cancer critically in molecular level which includes MYC genes (c-MYC and N-MYC, and L-MYC), HER-2/NEU genes, Tumor suppressor genes, p53 genes, RB genes and p16 and p15 genes.

Applications

In recent years peoples are attracted by the mangrove species due to its rich source of medicinal properties with lot of pharmaceutical application. But much attention needs to find out the remedy for this serious global problem with lung cancer to protect the human population.

Peer review

This is the excellent review given by the author. This may help to understand the global problem lung cancer and to know the importance of chemotherapy; sofar 45 different mangrove plants have the anti-cancer potential but not studied thoroughly. This study clearly indicates the much more bottomless study need to find out the remedy for this problem and mangrove may be very good source. Also UGC, Government of India supported this brilliant study.

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