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Review Article

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MOLECULAR PLAYERS OF LUNG CARCINOMA

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ABSTRACT

Lung cancer is a leading root of cancer related death worldwide. It is increasing at a very fast rate in both men and women. Among all types of cancers, lung cancer is the commonest cancer type in the world. Due to poor prognosis of lung cancer patients, shows resistant to different therapies. Initiation, progression and treatment of the lung cancer can be achieved by the genome and transcriptome expression profiling of lung carcinoma. The identification of genetic mutations become possible by highthrouput genomic technologies (HTGT) and these technologies identifies that how these genetic mutation drives the progression of lung cancer and also revealed about the different targeted therapies like tyrosine kinase inhibitors that were proposed their action to combat changes at molecular level. These technologies introduce the novel biomarker for the detection of lung cancer at early stage. These biomarkers can be used as the diagnostic, prognostic and therapeutic purposes. In this review we summarized about different novel genetic mutations such as ALK, EGFR, MET, KRAS etc. in lung carcinoma.

KEYWORDS: Lung Cancer, NSCLC, Inhibitor, Receptor tyrosine Kinase.

INTRODUCTION

Lung cancer is an increasing cause of cancer related mortality in the world in men and women both. According to WHO (2012) data, lung cancer is the most common in men and it is fourth most common in women globally in comparison to breast, colon and cervical cancer. Lung cancer covers about 19.4% of all cancer related mortality.[1] In 2015, Siegel RL et al. estimated that 28% men and 27% women deaths occur due to lung cancer in United States.[2] American Cancer Society had been estimated that there will be 221,200 patients of lung cancer with mortality of 158,040 due to this cancer. The survival rate is very poor, nearly 5 years in 17% of cases because of its late stage diagnosis.[2] Due to the high mortality rates of lung cancer, require to develop its treatment and diagnosis as soon as possible. Lung cancer is characterized into two category on the basis of the cell morphology, namely, non-small cell lung carcinoma (NSCLC) and Small cell lung carcinoma (SCLC). NSCLC reached up to 85% of all lung carcinoma. NSCLC subdivided into NSCL Adenocarcinoma, Large cell carcinoma and Squamous cell carcinoma.[3] In Indian scenario, lung cancer threat in 6.9 % of all cancer cases and 9.3% mortality in all types of cancer in men and women both.[4] There is 5 years overall survival rate in 15 % of cases in developed countries and 5% in developing countries.[5] Behind this type of cancer, several molecular mutations are involve like EGFR, ALK, MET, KRAS etc. and for the treatment of all these mutations, several targeted therapies are available (table-1). Before the treatment, the detection method should be gold standard for all types molecular mutations (table-1).

ALK (Anaplastic Lymphoma Kinase)

According to Sag et al. in 2016, ALK gene rearrangement and EGFR mutation detected in 1.96% in 51 cases and 14.39% in 132 cases respectively.[6] ALK gene present on a short (p) arm of chromosome number two at 23rd position (2p23). This gene encodes transmembrane receptor tyrosine kinase, which belongs to insulin like super family, which have extracellular, transmembrane and cytosolic kinase domain. Ligand binds to extracellular domain, which promote conformational change in the receptor and its cytosolic domain gets phosphorylated due to its kinase activity at tyrosine (Tyr) residue.[7] Generally ALK is involved in neuronal development.[8] It express during embryogenesis after that become still.[9] In most of the mutations, ALK involve by translocation with its partner genes.[10].

In 1994, first partner was NPM-ALK in Anaplastic Large Cell Lymphoma.[11] There are several fusion oncogene have been discovered with ALK, these are CLTCL1, ATIC, TFG, TPM3.[12] ALK mutation have been discovered in several carcinomas, namely esophageal

cancer, neuroblastoma, diffuse large B cell lymphoma, renal cell carcinoma, colon cancer, breast cancer including NSCLC.[13]

The ALK mutation in NSCLC discovered in 2007 by Soda et al., in which EML4 rearrangement was showing with ALK.[14] EML4 shows several break points because of this EML4-ALK mutation gives more than one variants such as V1,V2, V3a/V3b and V5a.[15,16] ALK gene rearrangement has been described with several partners, namely KIF5B, TFG, STRN, HIP1, BIRC6, SQSTM1 and KLC1.[17] Translocation of ALK gene trigger constitutive kinase activity of tyrosine kinase domain, leading to increase cell survival, cell proliferation, ultimately tumorogenesis. ALK signaling pathways include phospholipase Cγ, Janus kinase (JAK), mTOR, Sonic Hedgehog, STAT, PI3K, AKT and MAPK signaling cascades.[13] ALK mutation in NSCLC has been seen in never smokers, in mostly adenocarcinoma.[18] For the treatment of ALK mutated NSCLC cases, crizotinib have been approved by United States FDA in 2011 as a targeted therapeutic drug. This drug has also MET and ROS1 tyrosine kinase inhibition activity.[19] Most of patients show resistance against crizotinib within one to two year from the initiation of therapy.[20] After crizotinib, ceritinib developed, which gives very good response whenever crizotinib gets failed, so ceritinib treatment was approved for NSCLC in case of resistivity towards crizotinib.[21] More than one ALK mutation inhibitor is available, namely crizotinib, (first generation), ceretinib, brigatinib (AP26113) and alectinib (second generation inhibitor) and lorlatinib (third generation). Alectinib has inhibiting activity against ALK secondary mutation (L1196M) leading to crizotinib resistance. In all these inhibitor brigatinib is a powerful inhibitor of ALK and EGFR including ALK L1196 as well as EGFR T790M. The lorlatinib is a reversible ALK ATP competitive inhibitor and also of ROS1, this drug is also effective against all known resistant mutants.[22] Sag et al. (2016) noticed in a 54 year old female patient with wild type EGFR while ALK rearrangement was seen in smokers with NSCL adenocarcinoma histology.[6]

KRAS

KRAS (Kirsten rat sarcoma viral oncogene homolog) is first characterized oncogenes, belongs to the RAS family of oncogene together with NRAS and HRAS.[23] RAS has a GTP kinase activity, is invented in 1960s. The active form of RAS participate in the different signaling pathways of cellular processes.[24,25] Previously in 1984 KRAS mutation has been discovered in squamous cell lung carcinoma.[26] In some clinical trials 8-24% incidence rate have been found with KRAS mutation in NSCLC,[21] with higher proportion of NSCL adenocarcinoma.[25] There are several types of KRAS mutations have been diagnosed like G12C, G12V, G12D and G12A in near about 40%, 21%, 17%, 10% of cases respectively.[28] There are 25% to 35 % incidence rate of KRAS mutation in smokers and only 5% cases with non smoker history.[29,30] At present, G12D mutation of KRAS is about 56% in non smoker patients while G12C is 41% among current smokers and in former smokers. The possibility of G>A transition mutation is more in never smokers in comparison to current and former smokers, whereas in former and current smokers, the possibility of G>T nucleotide transversion mutation are very common.[28,31] KRAS present in downstream of EGFR signaling (figure-1) when KRAS become permanent active shows resistance to EGFR therapy. But in several other studies, it has been shown that lower efficacy of TKI therapy of EGFR in KRAS mutated NSCLC.[32,33] Generally EGFR and KRAS mutation are not found parallel but in a report of Benesova et al., EGFR and KRAS mutation are found along with each other and shows the positive response against gefetinib and erlotinib.[34]

NRAS mutation commonly present in lung adenocarcinoma, near about with 1% of NSCLC cases.[35]

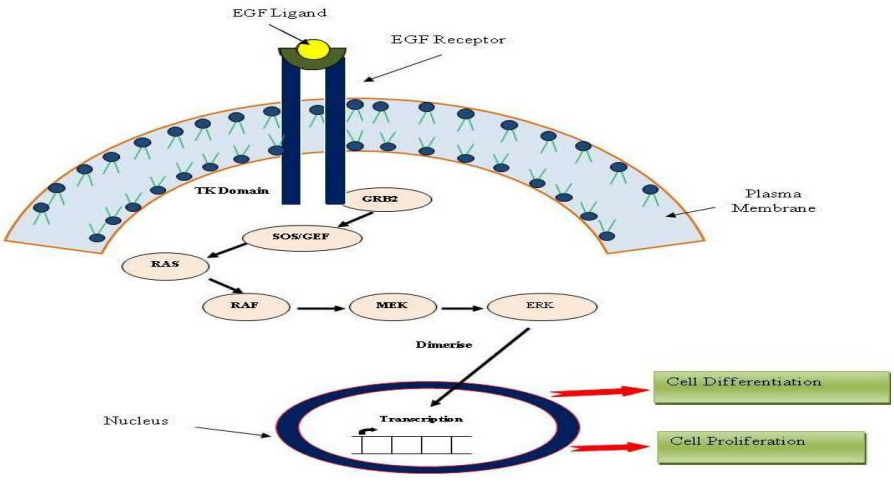

Figure 1. Showing the cascading of EGF receptor tyrosine kinase with downstream RAS protein in cell proliferation and cell differentiation (Modified from the review of Morgillo F et al. ESMO Open 2016;1:e000060)

MET

The MET (Mesenchymal-epidermal transition) gene is present on 7q312 chromosome, firstly it was discovered as a proto-oncogene in human osteogenic cell line in the year 1984 and later it was encoding a receptor tyrosine kinase known as c-MET or MET. Its ligand is hepatocyte growth factor (HGF) also known as scatter factor (SF) encoded by the gene present on long arm of the chromosome 7q21.1.[36] This RTK is made up of three types of domain such as extracellular of α chain and transmembrane of β chain and its C-terminal cytosolic domain, is a site of adaptor protein docking, such as GAB1 and GRB2 which promote downstream signal cascading through ERK, PI3K and STAT(figure-2).[37] The MET signaling regulate many cellular activities involving cellular proliferation, angiogenesis, cell invasion, cell motility, metastasis and epithelial to mesenchymal transition (EMT).[38] Alteration of MET can be promoted by genomic amplification, overexpression, alternative splicing in transformed cells.[39] MET amplification are present near about 2%-5% in NSCLC cases, largely with adenocarcinoma.[40] Onozato et al. in 2009 detected amplification in 21% of the cases of NSCLC in a Japanese study.[41] MET amplification shows in more than 25 % of the cases of NSCLC, with poor prognostication.[42] Ariyawutyakorn W. reviewed (in 2016) about six orally taken MET inhibitor, in which two have selective MET inhibiting property namely capmatinib and tivantinib and other four have multi kinase inhibiting property, amuvatinib, cabozantinib, crizotinib and foretinib.[43]

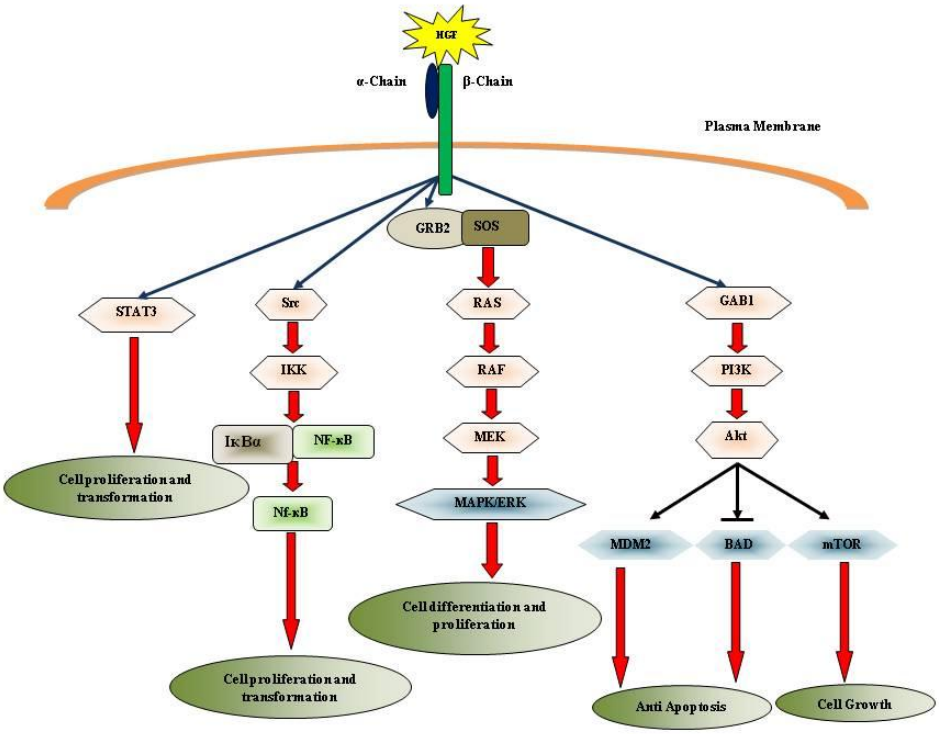

Figure 2. Showing different pathways involved in proliferation, growth, differentiation and in anti apoptosis of the cell (Modified from the review of Ariyawutyakorn W. et al. 2016).

EGFR (Epidermal Growth Factor Receptor)

EGFR is a transmembrane receptor tyrosine kinase, which belongs to ErbB family.[44] Its extracellular domain has amino terminal, made up of four domains in which domain III participate in ligand binding.[45] Intracellular kinase domain is a carboxyl terminal domain and, this kinase domain activated by ligand binding (EGF) to the extracellular domain of the EGFR, after binding of ligand to the receptor, it triggers the dimerization of the receptor and autophosphorylation of intracellular tyrosine kinase domain which recruit the signal cascading protein, results in the activation of cell differentiation and proliferation, cell survival and cell motility (figure-1).[46]

In different types of genetic driver mutations, EGFR mutation is very common in tumors of NSCLC patients. In the study of Doval DC et al. (2015), EGFR mutations was present in 32.8% of the NSCLC adenocarcinoma cases, significantly associated with sex and cigarette smoking.[47] In Indian scenario, into two different studies, represented the frequency of EGFR mutation were 25.9% and 51.8% respectively with the dominance in the females,[48] however studies have also reported the regional differences with the higher incidence rate (65%) in the southern Indian population while 33% in the north Indian population.[49] The eastern and western Indian population shows incidence rate of mutation of EGFR are 33% and 26 %.[50]

Exon 18 to 21 of tyrosine kinase domain on intracellular site, shows EGFR mutations, while 90% of it shows deletions in exon 19 and also the point mutation (L858R) in exon 21.[51] Gefetinib and erlotinib are two novel drugs which act as TKI, binds to ATP docking site on mutant EGFR.[52] Some mutations like small insertion or duplication in exon 20 or even in exon 19 and 21 shows the resistance to TKI of EGFR, moreover the other mutations, such as T790 (exon 20), L747S (exon 19), D761Y (exon 19) and T854A (exon 21) also show the resistant to the TKI.[53] Additionally some genetic mutations or alterations like PIK3CA mutation, loss of PTEN function, KRAS mutation, amplification of MET signaling and mutation in signaling of EGFR, consequently some investigators have made many strategies to conquer the resistance tyrosin kinase inhibitors of EGFR. TKIs of EGFR are not only crizotinib and gefetinib but also aflatinib and dicotinib, are under the investigation. It have been seen that aflatinib acts as an irreversible inhibitor of HER2 and EGFR.[54,55]

Table 1. Summary of lung cancer mutations, inhibitors and their detection methodology. (Modified table adapted from the review of Luo SY, et al.2014 and Carper MB, et al. 2015).

Genetic aberration	Targeted therapy	Detection methodology
ALK fusion	Crizotinib, alectinib, Ceretinib	Fluorescence insitu hybridization, Real- time reverse transcription-PCR, Immunohistochemistry (IHC)
EGFR mutation	Gefetinib afatinib erlotinib, AZD9291	Real-Time PCR, Direct Sequensing, High resolution melting amplicon analysis
KRAS mutation	Not Available	Real-Time PCR, Direct Sequensing, Restriction faragment length polymorphism (RFLP), Amplification refractory mutation system.
MET amplification	Tivantinib, Crizotinib, Cabozantinib, Ornatuzumab	Fluorescence in situ hybridization (FISH), PCR based sequencing, Quantitative PCR

DDR2 (Discoidin Domain Receptor 2)

Discoidin domain receptor 2 (DDR2) is a receptor tyrosine kinase, which is involve in cell proliferation, cell migration and cell adhesion also.[56] DDR2 mutation are present in non-small cell lung carcinoma in the frequency of near about 4%. There are multi tyrosine kinase inhibitors, namely dasatinib act against DDR2 in cell line of squamous cell carcinoma.[57] In recent the clinical trials are going on against DDR2 in NSCLCs.

Rare Genomic Mutation

MEK1 (or MAP2K1) belongs to a serine-threonine kinase family with near about 1% of mutations in non-small cell lung carcinoma, most of the cases in adenocarcinoma.[58] NTRIK1 is recently discovered in lung adenocarcinoma with non smoking patient history in approximately 3% of the cases. The NTRK1 gene involves in the encoding of nerve growth factor receptor. There are two fusion variants known as MPRIP-NTRK1 and CD74-NTRK, which have been shown to have oncogenic potential activity.[59] There is an inhibitor, RXDX-101 is taken up orally for TrkA, TrkB and TrkC and also for ALK, ROS1 mutations.[60]

CONCLUSION

Lung carcinoma is increasing vastly worldwide, because of its late stage diagnosis as well as poor prognosis too, so there is need of validated biomarkers for the early detection of lung carcinomas, which can be used to provide targeted therapies, will help in the increment of the survival of patients.

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