ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

MOLECULAR FACETS OF LUNG CANCER; FROM A PATHOPHYSIOLOGIC FACTOR TO THERAPEUTIC APPROACHES

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Abstract

Lung cancer has been the most common diagnosed cancer for the last several decades. It is the leading cause of cancer mortality worldwide and has a dismal prognosis owing to discovery of it at a late stage. The pathogenesis of lung cancer entails a build-up of many molecular malformations over a lengthy time .In recent years, there is significant advances in the understanding of the molecular biology that promotes lung cancer, which has resulted in a revolution in the diagnosis and treatment of lung cancer depending on an individual's tumor genotype. In this review article, we will give a highlight on the breakthrough the clinically relevant genetic changes in lung cancer including oncogene activation, tumor suppressor gene inactivation and other subscribed aspects that has the potential to open up new treatment avenues.

Keywords: lung cancer, molecular biology, biomarkers, mutations

Introduction

Globally, lung cancer has been the most common diagnosed cancer for the last several decades, it is the cancer number one in cancer-related death in men and the second- type of cancer in women following breast cancer. In 2018, 2.1 million new cases and 1.8 million deaths occurred (1.2 million in men and 576,100 in women), accounting for 1 in 5 cancer- related deaths worldwide. Prognosis of lung cancer is not good with a global survival rate of 15% in all stages because cases are presented late when tumors are unresectable. [1,2]

Hanahan and Weinberg delineated the 'Hallmarks of Cancer' as the attribute that normal cells slowly gain in their transformation activity to a tumor.[3] They described 6 hallmarks along with 2 other emerging findings and 2 enabling characteristics that facilitate growth of tumor. The six hallmarks are; maintain proliferative signaling, evading growth suppressors, provoking angiogenesis, allowing replicative immortality, overcoming cell death, enhancing invasion & metastasis. The other features are avoiding immune destruction, deregulation of cellular energetics, tumor promoting inflammation and genome instability and mutations.

Microsatellite modifications are the first molecular changes in the bronchial epithelium. Microsatellite changes are extension or deletions of tiny repeating DNA sequences that manifest as microsatellite instability (MSI or allele shift) or loss of heterozygosity (LOH) which is the absence of a normally present allele. For a cell to develop into cancer, 3 or more changes are required (figure 1).

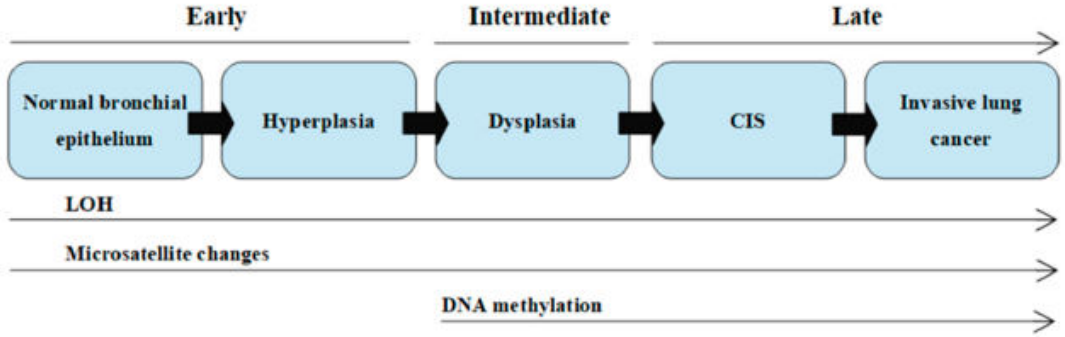

Figure (1). A simplified diagram depicting the molecular changes that occur during carcinogenesis [4]. LOS: loss of heterozygosity, CIS: carcinoma in situ.

Lung cancer is divided into two main types, non-small cell LC (NSCLC) and small cell LC (SCLC), whereas their prevalence is 80%-85% and15%-20%, respectively, they are recognized based on histologic, clinical, and neuroendocrine features. [5]

There is molecular differences in the 2 subtypes of lung cancer and in the subtypes of NSCLC also which include oncogenic mutations, gene amplification, increased protein expression, tumor suppressing alterations which include mutations, deletion and loss of heterozygocity, loss of protein

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

expression, tumor-acquired DNA methylation, chromosomal aberrations, and presence of telomerase activity.[6] Lung cancer is identified by a high tumor mutational burden (TMB) compared with other tumors which is most probably due to smoking.[7]. In a research study by Kan and colleagues ,[8] they discovered that (NSCLC) has the greatest rate of protein-altering mutations with rates in squamous cell carcinomas (SCCs) and adenocarcinomas and of 3.9 and 3.5 per mega base (Mb), respectively compared with an average rate of 1.8 per Mb of DNA across all tumor types.
The goal of this study was to compile a summary of what is known about genetic abnormalities in lung cancer that aid in diagnosis and treatment options.

Genetic abnormalities of lung cancer

There are two classes of cancer genes: oncogenes and tumor suppressor genes. Most oncogenes began as proto-oncogenes. The activation of oncogenes leads to uncontrolled cellular proliferation, and cells undergo oncogenic transformation. Tumor suppressor genes or antioncogenes are a group of genes controlling cell growth through inhibiting cellular proliferation and maintaining genome stability.[9]
Oncogenes interchange

Epidermal growth factor receptor (EGFR)
EGFR belongs to the ERBB family of tyrosine kinase receptors. The ERBB family is comprised of four receptor tyrosine kinases: ErbB-1 (also known as an epidermal growth factor [EGF] receptor), ErbB-2, ErbB-3, and ErbB-4. EGFR is comprised of three domains: a transmembrane domain; an extracellular domain with ligand binding site, and an intracellular domain with tyrosine kinase activity. Upon ligand binding, the receptors form homo-or hetero-dimers, enhancing activation, relaying signals for proliferation, survival, migration and differentiation and thus contributing a paramount part in cancer progression. Growth factor receptors: promising drug targets in cancer.[10] EGFR is overexpressed in 62% of NSCLCs, and mutations are seen in approximately 20%–30% of lung adenocarcinomas; however, it is very rarely seen in squamous cell carcinomas and not seen in SCLC. EGFR mutations are more common among women (42–62%, Asian populations (30–50%) and never-smoker patients (51–68%).[11] Activating somatic mutations are present in exons 18−21 of the tyrosine-kinase domain and deletions in exon 19 and the L858R point mutation in exon 21 occur in 90% of all *EGFR* mutations. A response rate of approximately 70% to EGFR-tyrosine kinase inhibitor (TKI) therapy (erlotinib, gefitinib, afatinib) has been occurred. [12]
However, a resistance to EGFR-TKI occur in cases of exon 20 insertions and the T790M substitution, osimertinib is currently approved for use in these patients.[13]
EGFR mutations are recognized by using gene sequencing methodologies and real-time polymerase chain reaction (PCR)-based assays.
KRAS (Kirsten rat sarcoma) mutations

KRAS is one of the three members of the so-called RAS family, along with HRAS and NRAS**.** All these members having vital roles in monitoring signaling pathways activity that control normal cell proliferation.[14] In one study, 25% to 35% of adenocarcinoma patients have KRAS mutation**,** mutations in codon 12 are the most frequently encountered (75% of the total), while 7% have mutations in codon 13. [15]It is very rarely seen in squamous cell carcinoma or small cell cancer. KRAS mutations existence may be linked to a poor prognosis and could be a negative predictor of treatment response. Trials to use guided-therapies to target this mutation-phenotype have been unfortunately frustrating up to now. [16]
BRAF mutations

BRAF encodes a protein called B-Raf that accounts for a pivotal step in the RAS-mitogen activated protein kinase (RAS-MAPK) signal pathway. BRAF mutations are existing in 7–10% of patients with adenocarcinoma, current or former smoker. The most frequent of these mutations are distinguished by the substitution of valine by glutamate (Val600Glu or V600E) in exon 15. BRAF inhibitors like vemurafenib and dabrafenib are highly effective and selective against the V600E-mutant BRAF kinase, with overall response rate ranging from 33% to 42%.[17]
MET (mesenchymal epithelial transition) alterations

The MET gene is located on the long arm of chromosome 7 at position 31. This oncogene encodes for a tyrosine kinase receptor (hepatocyte growth factor receptor), which starts up multiple signaling pathways that take part roles in cell proliferation, survival, and invasion. Mutation, gene amplification

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

and protein overexpression are all examples of pathologic MET activation. MET mutations occurring in 3% of squamous cell lung cancers and 8% of lung adenocarcinomas. While, MET amplifications are found in 4% of lung adenocarcinomas and 1% of squamous cell lung cancers and are associated with sensitivity to MET inhibitors like capmatinib and crizotinib.[18]

Fibroblast growth factor receptor (FGFR)

FGFR gene encodes for a tyrosine kinase receptor belonging to the FGFR family. The FGFR family includes four receptor tyrosine kinases (FGFRs 1–4). The incidence of FGFR1 amplification is significantly higher in squamous cell carcinoma (20%) compared with adenocarcinoma (3%) and SCLC (5%). There are ongoing studies concerning the efficacy of the new FGFR1 inhibitor ponatinib .[19]

Discoidin Domain Receptor Tyrosine Kinase 2(DDR2)

It encodes for a tyrosine kinase receptor that is expressed in mesenchymal tissues and that binds fibrillar collagen as ligand. DDR2 activates important signaling pathways and promotes cell migration, proliferation, and survival. lDDR2 mutations have been reported in 3% to 4% of lung squamous cell carcinomas compared with

0.5% of adenocarcinomas. These mutations have been associated with response to dasatinib (a multitargeted kinase inhibitor). [20]

Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA)

The PIK3CA gene encodes for the catalytic subunit p110 alpha of P13Ks. PIK3CA amplifications, deletions, and somatic missense mutations have been described in many tumors including lung cancers. Mutations are found in 1% to 4% of patients with NSCLC, usually affecting exons 9 and 20 (80%). PIK3CA amplifications are more common in squamous cell carcinomas (33%) than adenocarcinoma (6%) and SCLC (4%). [21]

Human epidermal growth factor receptor 2 (HER2)

The human epidermal growth factor receptor 2 gene HER2 (ERBB2) is a proto-oncogene that encodes for a tyrosine kinase receptor member of the ERBB receptor family. HER2 lacks a specific ligand. Nevertheless, it can be combined with other ERBB receptors to form a heterodimer. HER2 expression and/or amplification is found in many cancers including lung cancer. Overexpression of HER2 has been described in 7% to 34.9% of NSCLCs and has been associated with poor prognosis.

Previous studies on HER2-targeted therapies (afatinib and trastuzumab), have shown a response rates of approximately 50% .[22]

Translocations

Translocations are structural rearrangements in the genome that bring 2 previously non-adjacent regions together. When two genes that are normally separated are brought together, the outcome can be an abnormal fusion protein synthesis. [23]Fusion proteins contribute to oncogenesis by inactivating tumor suppressors (such as TP73) or activating oncogenes abnormally. [24]

ALK (anaplastic lymphoma kinase) translocations

The ALK gene is found on chromosome 2 and encodes a transmembrane tyrosine kinase, ALK gene rearrangement occurs in ∼3%–5% of adenocarcinomas. Different ALK fusions have been described, most of them is ALK fuses with EML4 encoding (echinoderm microtubule associated protein like 4) to exons 20–29 of ALK, resulting in the production of a protein with constitutive ALK activity. Most of patients have ALK rearrangement are young, women, never-smokers and, showing peripheral tumors.[25]

The ALK tyrosine kinase inhibitor crizotinib is effective in patients whose tumours show an ALK gene rearrangement. Current diagnostic approaches to detect ALK fusion genes and their results include break-apart fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse-transcription PCR (RT-PCR).[26]

ROS Proto-oncogene 1, Receptor Tyrosine Kinase

ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) is a tyrosine kinase receptor member of the insulin receptor family. It is involved in downstream signaling processes involved in cell growth and differentiation. About 1% to 2% of NSCLCs harbor ROS1 rearrangements. ROS1-rearranged NSCLC typically occurs in young, female, never-smokers with a histologic diagnosis of adenocarcinoma and is usually mutually exclusive with other oncogenic drivers (EGFR, KRAS, ALK). Clinical trials have delineated that patients with advanced NSCLC harboring ROS1 rearrangement have gained from crizotinib treatment, showing response rates up to 80%.[27]

RET (REarranged during Transfection)

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

It encodes for a tyrosine kinase receptor for the glial cell line–derived neurotrophic factor family of ligands and is involved in cell proliferation, migration, differentiation, and neuronal navigation. Approximately 1% to 2% of NSCLCs harbor RET fusions. RET-rearranged NSCLC typically occurs in adenocarcinomas with more poorly differentiated solid features in young never-smokers**.** Preliminary studies with cabozantinib (MET and vascular endothelial growth factor receptor 2 inhibitor) in RET-rearranged lung adenocarcinoma are promising**.**[28]

Tumor suppressor genes changes

TP53 Gene (Tissue protein 53)

The *TP53* gene is located on chromosome 17 that codes for a 53-kDa protein .The Tp53 protein is a negative regulator of cell proliferation and a positive regulator of apoptosis in response to DNA damaging agents**.** Inactivation of TP53 is seen in 90% of small cell carcinomas and in approximately 65% of NSCLCs [29] more commonly in squamous cell than adenocarcinoma. *TP53* gene mutations can occur in association with *EGFR* and *KRAS* mutations. Previous phase I studies have tested the safety, biological effect and multiple methods of delivery of adenoviral-mediated p53 gene therapy in various tumors including lung cancer by inducing cell cycle arrest and apoptosis . When injected intra-tumorally, wild type p53 (wt-p53) was found to be expressed in patients with p53 mutations and three out of seven patients had tumor size reduction. [30]

Phosphatase and TENsin Homolog (PTEN)

It is a classical tumor suppressor gene located in the 10q23 region of chromosome 10 that inhibits the PI3K/AKT/mTOR signaling pathway**.** Decreased PTEN expression levels are seen in approximately 75% of NSCLC. PTEN mutations are seen in approximately 5% of NSCLC. It is more common in squamous cell carcinoma compared to adenocarcinoma and is associated with a history of smoking**.** Vandetanib,a TKI, has been efficacious against EGFR mutation‐positive lung cancer cell lines showing loss of PTEN.[31]

Liver kinase B1(LKB1)

It is also known as serine/threonine kinase 11 (STK11), it is a tumor suppressor gene that has been implicated in multiple biological processes including regulation of the cell cycle, chromatin remodeling, cell polarity, and energy metabolism**.** In lung cancer, *LKB1* may be inhibited by variable somatic mutations or deletions that produce truncated proteins with inactivation of *LKB1* occurring in about 11-30% of adenocarcinoma making it the third commonest genetic aberration in lung adenocarcinoma after *TP53* and KRAS**.**[32]

$p16^{INK4a}$

The p16INK4A/RB pathway regulates cell cycle progression from G1 to S phase. Retinoblastoma 1 (RB1) is a tumor suppressor gene that produces the RB protein, which regulates the G1/S transition in the cell cycle by interacting to the transcription factor E2F1. The pathway is primarily shut down in NSCLC because of changes in cyclin D1, CDK4 and the cyclin dependent kinase inhibitor p16(CDKN2A).[33] $p16^{INK4a}$ prevents the cell cycle progression through the G1/S checkpoint by inhibiting cyclin D1 dependent phosphorylation of RB protein**.** $p16^{INK4a}$ is inactivated in approximately 80% of NSCLC and was changed in 72% of squamous cell carcinoma, largely due to homozygous deletion, methylation or inactivating mutations**.** [34]

Survivin as a member of inhibitor of apoptosis proteins

Through direct binding to caspases, a family of proteins known as inhibitor of apoptosis proteins (IAPS) can prevent the apoptosis process. The baculoviral IAP repeat (BIR) is a domain of about 70 amino acids found in all IAP family proteins. The mammalian genome encodes 8 members of the IAP family. The BIRC5 member, also known as survivin. [35]

Survivin is expressed in all human tumor lines , with the highest levels in breast and lung cancer cells and the lowest levels in kidney cancer cells, according to the National Cancer Institute's (NIC) cancer drug-screening programme. [36]Survivin plays a role in carcinogenesis through variable methods, including apoptosis inhibition, cytokinesis and cell cycle regulation and engagement in a number of signaling networks, including the p53, Wnt 'Wingless/Integrated', hypoxia, Transforming growth factor (TGF) and Notch signaling pathways (Figure 2). [37]

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

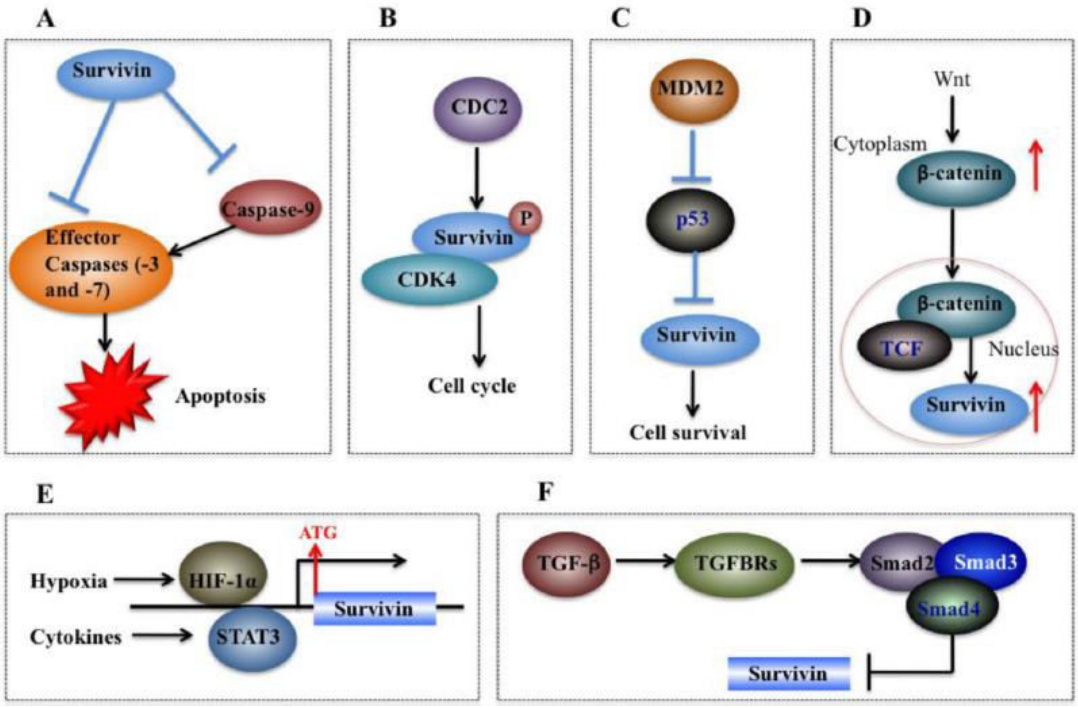

Figure (2). Molecular mechanisms of survivin in tumorigenesis. ***(A)*** *Survivin binds and suppresses effector caspases (caspase-3 and 7) and caspase-9, thereby resulting in decreased apoptosis in cancer cells.* ***(B)*** *CDC2 can directly phosphorylate survivin. Survivin also interacts with CDK4, which results in nuclear translocation,thereby leading to S phase shift.* ***(C)*** *Wild-type p53 represses survivin expression at the transcriptional level.* ***(D)*** *Activation of the Wnt signaling pathway leads to accumulation of β-catenin in the cytoplasm, which then translocates to the nucleus to form the β-catenin/TCF enhancer factor transcriptional machinery and upregulate survivin.* ***(E)*** *Both HIF-1α and STAT3 can directly bind to the survivin promoter and function as transcriptional activators of the survivin gene.* ***(F)*** *TGF-β is a negative regulator of survivin. The TGF signaling pathway transcriptionally downregulates survivin expression through a mechanism dependent on Smads 2, 3, and 4.*[38]

CDC2 :cell division cycle 2, CDK4: cyclin-dependent kinase 4, MDM2:murine double minute 2 , TCF ***:****T cell factor,HIF-1α : Hypoxia-Inducible Factor (HIF)-1, STAT3****:****Signal transducer and activator of transcription 3, ATG: autophagy-related genes, TGFBRs: transforming growth factor beta receptors.*

Four types of survivin-targeting techniques have been developed to improve tumor cell sensitivity to apoptosis and decrease tumor growth. These are some of the promising approaches : (1) antisense oligonucleotides , ribozymes, and short – interfering RNA (siRNAS) as transcription inhibitors; (2) post-translational inhibitors of survivin ; (3) surviving- based vaccinations; and (4) gene therapy techniques using surviving suppressor mutants .[39]

Chromosomal aberrations

Chromosome aberrations include changes in chromosome number (gains and losses) and changes in structure (deletions, inversions, and amplifications). Cancer cells have variable chromosomal abnormalities, including deletions , amplification and mutations.[40] Comparative genomic hybridization (CGH) analysis revealed patterns of chromosomal copy number aberrations in squamous carcinoma of the lung with amplified areas on chromosomal arms 1q,3q,5p, 8q,11q,12p,17q, 20q and 3q26 being particularly common.[41]

Splicing Alterations

Splicing is the process of removing introns between adjacent exons from transcribed premessenger RNA and joining the exons together.[42]

Alternate splicing refers to the ability of cells to change which exons are included in the final messenger RNA molecule. This allows them to produce many isoforms of the same protein from a single gene, resulting in a high proteome diversity level. Alternate splicing is strictly regulated in cells, but it is frequently unregulated in cancer cells. Mutations in genes that govern splicing, such as U2AF1

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

, or mutations in specific regions within the gene, such as splice site mutations , that the splicing machinery utilizes to identify and process introns and exons , can cause splicing deregulation. [43]
Some of samples of lung adenocarcinoma showed abnormal splicing of oncogenes such as CTNNB(β-catenin) and MET. [43]
Although mutations in the splicing factor U2AF1 were linked to improper splicing in CTNNB, abnormal splicing in MET was primarily due to splice site alterations within the gene. Exon 14 is excluded from MET messenger RNA due to splice site alterations in MET, which have been found in about 3% of non-squamous lung tumors.[44]
In these malignancies, there is rising clinical evidence that tyrosine kinase inhibitors such as crizotinib and cabozantinib , may be beneficial.[18]

Epigenetic alterations

Other mechanisms that are involved in lung cancer development are epigenetic ones. Epigenetic changes are heritable changes that influence gene expression and other DNA dependent processes without really changing DNA sequence. [45] These changes including DNA methylation, histone modifications, and non-coding RNA expression, specifically microRNA expression**.** Tumor suppressor gene inactivation through promoter methylation, often referred to as hypermethylation, is a hallmark of lung cancer and is an early event in the carcinogenic process.[46] Perception of different epigenetic changes count in different lung cancer types expands their utility of diagnostic and prognostic biomarkers for risk assessment, and early detection. MicroRNAs (miRNAs measured either from tumor samples or in biofluids, have emerged as biomarkers for tumor diagnosis, prognosis and prediction of response to treatment. Epigenetic alteration is reversible and can be reversed by different pharmacologic approaches, like hypomethylating agents and histone deacetylase inhibitors (HDACIs). FDA approved 6 drugs that target the epigenome (azacitidine, decitabine as hypermethylation inhibitors, vorinostat, romidepsin , panobinostat and belinostat as histone deacetylase inhibitors).[47]

Conclusion and future perspective

Lung cancer, a disease with a poor prognosis and a mortality toll of thousands of cases per year, is one of the most important diseases for which pathophysiological aspects must be understood. The signal pathways regulated by oncogenes and tumor suppressor genes, as well as epigenetic alterations involved in carcinogenesis, are complex and should be better understood in order to develop individualized specialized treatment options and determine early diagnostic and prognostic markers for lung cancer. These findings highlight the intricacy of lung cancer's molecular biology, making it difficult to develop effective targeted treatments. Although the introduction of targeted medicines has improved survival in a fraction of lung cancer patients, many of them continue to have poor outcomes, necessitating the development of novel therapeutic approaches on multiple carcinogenesis levels to enhance survival in these patients.

Acknowledgements

The authors would like to thank Chen X and colleagues [38] for allowing the use of figure (2) in this review article, their article is cited 224 times

Conflict of interest

None declared

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