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NON-CODING RNAs AND LUNG CANCER

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ABSTRACT: Lung cancer (LC) represents a significant global contributor to mortality, particularly for those between the ages of 40 and 50. Additional evidence for this predicament comes from the yearly rise in new LC cases and the disease's dismal 5-year survival rate of fewer than 15%. Even though smoking has been linked to a significant portion of Lung Cancer cases, a sizable number of non-smokers also contract the condition, raising the possibility that LC development may have hereditary and epigenetic roots. The genome only has about 1% of coding regions. As a result, scientists have studied the genome's noncoding region and discovered that noncoding RNAs are crucial to the etiology of lung cancer. In more detail, lncRNAs and miRNAs have been extensively investigated over several decades of research. The function of miRNAs in post-transcriptional gene regulation is widely known and understood. It has also been demonstrated that the antagonistic interaction between lncRNAs and miRNAs further regulates gene expression in both healthy and disease situations, including Lung Cancer. A circular RNAs study, which has received fresh interest recently, revealed that circRNAs can function as molecular sponges for miRNAs thereby regulating transcriptional regulation. Thus, it appears that circRNAs, lncRNAs and miRNAs work together in a circuit to best decide which gene in a biological system needs to be upregulated or downregulated. This review highlights this non-coding RNAs significance in the context of lung cancer development.

INTRODUCTION: Compared to the hypothesis that underpinned contemporary molecular biology, the world of RNA is significantly more complicated [1]. Coding RNAs and Non-Coding RNAs are two categories of RNAs that comprise RNA universe.

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Enzymes, cell structures, signal transducers, and other components are formed by proteins that are encoded by coding RNAs, sometimes referred to as messenger RNAs (mRNAs) [2].

Just 3% of the genome is made up of RNA that codes for proteins; the other 97% is known as the "dark matter" of molecular biology and is mostly in charge of regulating phenotypic [3]. Over time, it became evident that different RNA species are translated from the genome's "black matter" [4]. Only two percentage of the human DNA encodes proteins, yet more than 90% of the genetic material undergoes transcription, indicating that the

predominant portion of transcriptome comprises non-coding (ncRNAs) that necessitate an open reading frame and consequently, do not encode proteins [5]. Rather than suggesting that non-coding RNAs are functionally inert, it highlights the importance of extending our knowledge of normal and disease biology beyond the realm of protein-coding genes [6].

A large portion of non-coding RNAs (ncRNAs) execute crucial roles in cellular processes, including those performed by transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) in the process of translation of messenger RNA molecules (mRNAs), small nuclear RNAs (snRNAs) in splicing, small nucleolar RNAs (snoRNAs) in the modification of ribosomal RNAs (rRNAs) structure, and long non-coding RNAs [7]. The link between non-coding RNAs and lung cancer has been the focus of much research over the last few decades [8]. Lung cancer has the highest incidence rate for both sexes globally, representing 11.6% of every cancer diagnosis, and it also leads in cancer-related mortality, contributing to 18.4% of all cancer deaths worldwide [9]. Both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are different kinds of lung cancer. Of these, NSCLC accounts for about 85% of scenarios, over 80% of diagnoses, and contributes to more than one million deaths annually worldwide, making it one of the most lethal malignancies [10]. Lung adenocarcinoma, big cellular cancer, and pulmonary squamous cell carcinoma is three different subtypes of NSCLC that distinguished by their pathological features [11].

In 2020, there will likely be around 228,820 newly diagnosed cases of cancer in the USA, and up to 135,720 fatalities attributable to the disease. In 15% of SCLC patients, the main form of LC is detected. The majority of SCLC cases have been associated with cigarette smoking [12]. The body uses non-coding RNAs (ncRNAs) for a number of physiological and pathological functions, and the emergence of illnesses including cancer, neurological diseases, and cardiovascular ailments is closely associated with ncRNA dysregulation [13]. The proliferation, stemness, metabolism, differentiation, apoptosis, invasion, and treatment resistance of tumor cells can all be controlled by non-coding RNAs (ncRNAs), and their dysregulation can be influenced by tumor cell gene mutations or epigenetic modifications [14]. The interaction between tumor cells and stromal cells can be mediated by ncRNAs through a variety of methods to either promote or inhibit tumor progression, which is even more significant [15]. This study reviews recent studies on lung cancer and aims to elucidate the role of the ncRNAs.

Non-Coding RNAs (ncRNAs):

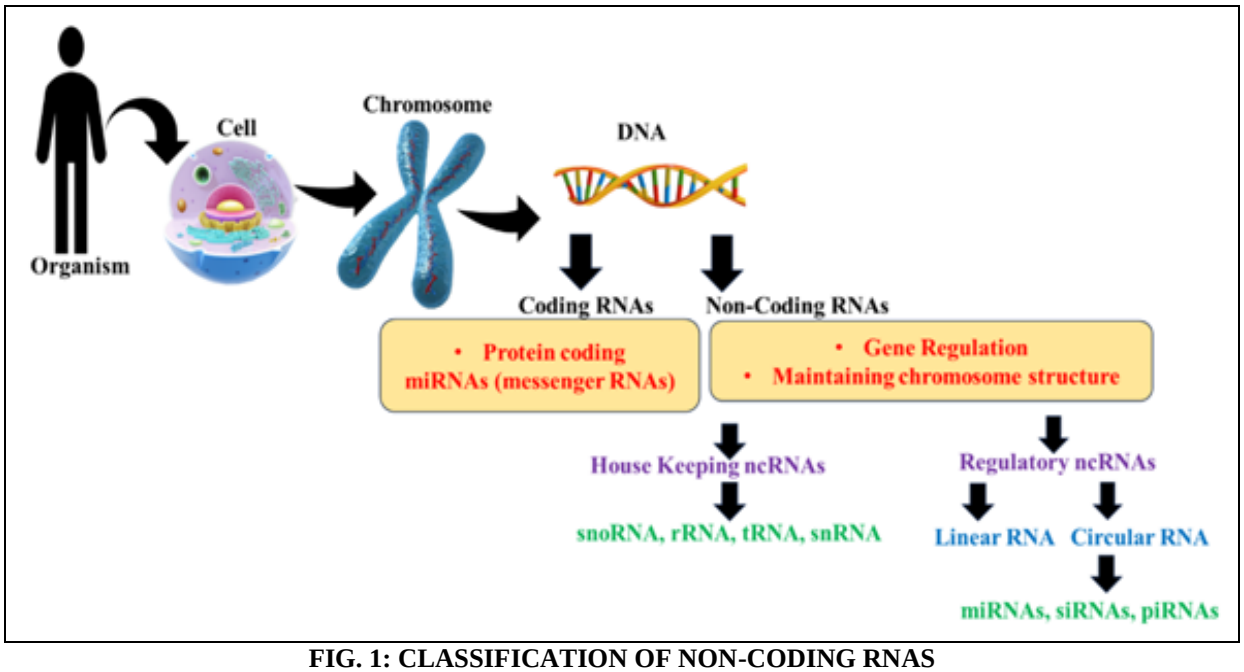

FIG. 1: CLASSIFICATION OF NON-CODING RNAS

All living organisms depend on the regulation of gene expression, which is necessary for formation and upkeep of homeostasis in cells and tissues [16]. Francis Crick's "central dogma" claimed that messenger RNA (mRNA), a messenger molecule, translates genetic data derived from DNA before it translated into proteins [17]. In this perspective, proteins have been thought of as functional products of genetic information for several years even though only 2% of human genes can be translated into proteins and approx 80 percent of the human DNA could be transcribed as RNA [18]. Recent developments in sequencing methods have led to the identification of more important RNAs with little to no coding potential [19].

While the exact biological role of this class of RNAs remains unclear, increasing amounts of non-coding RNAs (ncRNAs), that make up over 60% of a human cell's transcriptional output, have shown a regulatory role in a variety of biological processes that occur within the cell [20]. No protein-coding potential and poor Kozak sequencing for protein translation initiation are two characteristics of ncRNAs and approximately much of mankind's genome 97% is not coded [21]. All types of cells express ubiquitously housekeeping non-coding RNAs, including tiny nuclear RNAs, transfer RNAs, ribosomal RNAs, and short nucleolar RNAs. rRNAs and tRNAs are two different RNA types that make up mRNA [22].

Recently, scientists have become interested in a separate family of non-coding RNAs because of their regulatory roles. There are two categories for these regulatory ncRNAs: Short non-coding RNAs (sncRNAs), are the first class of linear RNAs. They are comprised of 18 to 25 nucleotides. In contrast, **Fig. 1** shows that circular RNAs (circRNAs) are ranked second by long non-coding RNAs, which have a nucleotide count exceeding 200 [23]. The field of regulating non-coding RNAs, which comprise circRNAs, lncRNAs, and sncRNAs, has experienced a notable surge in attention in the past few years. This is because of their conditional expression, tissue-specificity, and variety of modes of action, all of which point to them as biological markers and targets [24]. There is evidence to support the hypothesis that non-coding RNAs (ncRNAs) can serve as prognostic and diagnostic biomarkers for several cancers, including lung cancer [25].

The placenta is an essential organ created during pregnancy that serves as both the barrier and the link between the mother and the fetus. Placentation is thought to be regulated at the molecular level. The main components of this regulation are proteins and the specific gene expression controls that go along with them. A large fraction of this regulation functions through RNA-level interactions on the post-transcriptional level, mainly through ncRNAs [26].

Non-coding RNA (ncRNAs) Applications: When producing an RNA product suitable for pharmaceutical application, several considerations must be made, such as the required amount, the product's quality, stability, safety, and biological activity until it reaches the target location (nucleus, cytoplasm, or particular organelles) [27]. Thus, to go forward with using RNA as biopharmaceuticals, the problems pertaining to its production, purification, stability, and transportation must be resolved [28]. Because of the diversity of RNAs, their biological functions, and most notably, their potential utility in the biomedical field, it is imperative to establish efficient procedures for their synthesis [29]. Now, RNAs may be made in three distinct ways: *in-vivo* (recombinant), enzymatic, and chemical [30].

The most widely used method for making RNA is chemical synthesis, which creates oligonucleotides automatically using phosphoramiditechemistry [31]. Overall, it is evident that discoveries in the processes used to create, purify, stabilize, and administer this biopharmaceutical will be crucial to the development of RNA as a therapeutic agent, as will our understanding of the disease-related molecular mechanisms connected to RNA dysregulation. The actual conjugation of efforts from interdisciplinary teams, bringing together professionals in biology, molecular biology, biochemistry, biotechnology, and pharmaceutical sciences, can provide solutions to the difficulties stated [32].

Long Non-Coding RNAs: RNA realm hypothesis intends that the early life growth would have been through an established ribonucleic acid which afterward developed the depository of the facts into the more stable genetic element, DNA [33]. Initially, in higher animals, the major portion of the DNA

was presumed to be junk with no catalytic or structural role [34] but the findings related to small non-coding RNAs like miRNAs (microRNA), piRNAs, and snoRNAs associated with important cellular metabolic processes have changed this perception [35]. Furthermore, over 70% of human DNA is involved in the normal functioning of many cells, as demonstrated by the discoveries made over the past 20 years regarding long-non-coding RNAs (lncRNAs) and their vital function in these processes [36].

It has been reported that the lncRNAs are above 200 nucleotides long and do not convert into any useful polypeptides [37]. Based on different criteria these lncRNAs can be categorized in different ways based on their genomic position they are of five types, namely sense, antisense, bidirectional, intronic, and intergenic lncRNAs [38]. Furthermore, depending on their biological roles, they may be divided into some groups. First, transcriptional regulators that help to promote TCF21 expression include lncRNA TARID, which creates an R-loop and attracts GADD45A (39), APOLO (Auxin Regulated Promotor Loop RNA), which performs ruse for LHP1 at the R-loop and governs the activity of auxin-responsive genes, and ANRIL, which seeks PRCs (Polycomb repressive complexes) to those who promote of CDKN2A and CDKN2B to block their activity in cis and to control distant genes in trans-LINC-PINT HOTTIP increases the synthesis of HOXA genes, it suppresses the transcriptional activity hallmark of malignant cell invasion, and lncPRESS1 functions as a deception to deceive sirtuin 6 into regulating gene expression, Regarding Post-Trasncriptional regulation, PNUTS sequesters miR-205, which causes ZEB1 and ZEB2 mRNAs to be upregulated and encourages the epithelial-mesenchymal transition.

In contrast, PNCTR binds to PTBP1 and prevents splicing that PTBP1 controls. To initiate translation, AS-uchl1 binds to Uchl1 mRNA. Regarding structural roles, NEAT1 is a scaffold lncRNA found in paraspeckles, MALAT1 interacts with RBFOX2 and controls mRNA splicing. It also modifies the phosphorylation of SR protein in nuclear speckles and sno-lncRNAs, Genome integrity-GUARDIN, a long non-coding regulatory promoter of miR34a, functions as a sponge for miR-23a in telomere function and stabilizes BRCA1 to enable DNA repair [40]. How these lncRNAs function to demonstrate their impact on regulating the metabolic processes of the cell are diverse? MicroRNA (miR-50-3p, miR-200b-3p) is sucked up by lncRNAs such as lncRNA UCA1, lncRNA H19, lncRNA OIP5-AS1, lncRNA SNHG16, and lncRNA XIST, which in turn controls the microRNA-mediated downregulation of mRNA. Ribonucleoproteins are supported by lncRNAs. LINP1 (lncRNA in non-homologous End Joining Pathway 1) and TERC (telomerase RNA component) are two examples of these scaffolds. LncRNAs such as CR11538, SOX1-OTV1, and LINC00926, which remove genomic regulatory regions, function as ruses [41]. RNAs that function as guide RNAs, such as HOTAIR and CCAT1, can either up- or down-regulate the expression of a gene by drawing additional molecules, like proteins, to a particular region of a nucleic acid shown in **Fig. 2**. Guided lncRNAs are encouraged to target specific targets by RNA-DNA, RNA-RNA, and RNA-Protein. Gene regulation is aided by chromatin loops, which are created by LncRNA [42].

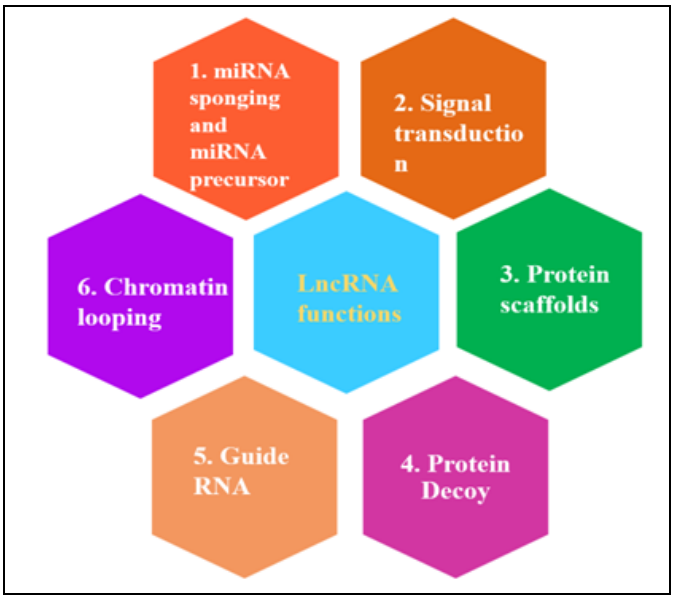

FIG. 2: FUNCTIONS OF LONG NON-CODING RNAs (LncRNAs)

According to recent research, non-coding RNAs are essential for the growth and homeostasis of skeletal muscle, as well as for the development of muscular disorders, Parkinson's disease, and sarcopenia in particular [43] Parkinson's illness can be accurately diagnosed using long noncoding RNAs

(lncRNAs). By inhibiting the death of neuronal cells and the generation of inflammatory cytokines, RMST downregulation targeting miR-150-5p may regulate the start and course of Parkinson's disease (PD) (50%). Between moderate and severe patients, the expression of LncRNAs NEAT1 and MALAT1 varied dramatically in numerous cell types, indicating that these might be markers of immunological dysfunction in COVID-19 and potential targets for testing or treatment according to severity [44].

Long Non-Coding RNAS and Lung Cancer:

LncRNAs as Prognostic Indicators in Lung Cancer:

Chemotherapeutic Sensitivity: It is typically possible to perform surgery on the original tumor in an eligible patient with the initial stages of non-small cellular lung carcinoma before the cancer cells penetrate or disseminate. Unfortunately, between 30 and 35 percent of individuals with stage 1 NSCLC will recur following surgery. Clinical data on chemotherapy as an adjuvant after NSCLC resection showed that among 1867 individuals, 44.5% had a relative survival rate of five years after receiving chemotherapy; this was significantly greater than the 40.4% in the control group. Additionally, the investigation showed that the administration of additional chemotherapy following resection by surgery results in 7000 fewer NSCLC patient deaths yearly. The survival of individuals with NSCLC in stages II and IIIA has been documented in several different clinical trials. The relative survival rate of five years increased by 8%–15% after adjuvant cisplatin-based therapy [45].

Therefore, after surgical removal, additional chemotherapy has consequently been demonstrated to benefit individuals with initial-stage lung carcinoma. Inevitably, one of the primary causes of the low therapeutic efficacy in non-small cellular lung carcinoma (NSCLC) is the development of chemical resistance of the cancerous growth during therapy. LncRNAs have been studied as a potential predictor of chemosensitivity, which might aid in determining the optimal course of treatment for individuals with lung cancer. Several lncRNAs has been suggested as prognostic indicators that may influence the chemosensitivity of individuals with lung cancer [46].

Signaling Pathways Related to Chemo-sensitivity: Chemotherapy is thought to be a crucial adjuvant treatment for many NSCLC patients following surgical tumor excision. However, patients frequently become resistant to medications like paclitaxel and cisplatin throughout chemotherapy. Therefore, understanding the fundamental causes of chemotherapy resistance is crucial to increasing the treatment's effectiveness. LncRNAs mainly use the following pathways to control the drug sensitivity of cancerous cells in the lung: Signaling pathways that impact cancer cell stemness include 1) the MAPK/ERK route; 2) the PI3K/PKB/mTOR (PKB also referred to as AKT) and signaling pathway of Nuclear factor-κB; 3) the mitochondrial pathway; 4) the Siganl transducer and activator of transcription 3 (STAT3) signaling pathway; and 5) the control of the Wnt/β-catenin signaling system. 6) Multidrug resistance (MDR); 7) the epithelial-to-mesenchymal transition (EMT); 8) autophagy; and 9) the interaction between apoptosis and autophagy to activate or deactivate Beclin-1 (47).

For NSCLC patients, the relative survival rate of five years is usually quite poor since 60–80% of them do not obtain a diagnosis until the disease has advanced. Chemotherapy and radiation therapy together can reduce distant tumor metastases from non-small cell lung cancer (NSCLC) and increase patient survival. However, much like chemotherapy, the radioresistance of lung cancer cells limits the effectiveness of radiation. A few lncRNAs are allegedly prognostic markers of lung cancer's radiosensitivity [48].

Signaling Pathways Associated with Radiosensitivity: Three major routes influence lung cancer cells' radiosensitivity. One of these is known as apoptosis. Numerous cancer therapies, such as radiation therapy, promote the procedure of apoptosis, which results in the death of tumor cells. Apoptotic pathways comprise an inherent channel of the mitochondrial-driven apoptotic process (mitochondrial route) and an extrinsic mechanism of apoptosis mediated by death receptors [49]. By preventing the pro-apoptotic protein Bax from moving from the cytoplasm to the mitochondrial outer membrane and activating caspase-9 and caspase-3, the anti-apoptotic protein Bcl-2 restricts the intrinsic mechanism of

mitochondrial-mediated apoptosis [50]. Note that autophagy and apoptosis have a tight association; this is another mechanism of radiosensitivity. The protein Bcl-2 suppresses autophagy. It has been found that autophagy can prevent apoptosis and is increased in radioresistant cancer cells [51]. One aspect that may impact the effectiveness of radiation therapy is the degree of oxygen deficiency (hypoxia) present in tumor tissue. Under hypoxic conditions, HIF-1 signaling pathway increases autophagy, which aids tumor cells alive. The EMT mechanism is the third. The overexpression of matrix metallopeptidase 2 (MMP-2) and matrix metallopeptidase 9 (MMP-9) facilitates the migration of lung tumor cells. Mesenchymal phenotypic markers like vimentin and N-cadherin are overexpressed in EMT, while epithelial phenotypic markers like E-cadherin are lost. EMT is one element that makes up radioresistance. Lung cancer patients with EMT have a very poor prognosis [52].

EGFR-targeted Therapy Sensitivity: Tyrosine kinase activity enables the receptor to attach to the epidermal growth factor (EGF). EGF regulates several physiological processes, including cell division, proliferation, migration, and growth. Statistical analysis of information from huge cohorts has demonstrated the diversity of cancer types. EGFR protein expression is more prevalent in the tissues of certain diseases, such as lung cancers than in normal tissues [53]. In other cohorts, 40–80% of NSCLC patients have tumors that show EGFR dysregulation. EGFR mutations are recognized to be a contributing factor for the development of NSCLC, and they are commonly found to occur in exons 19 and 21. For individuals who have EGFR mutations in lung carcinoma, targeted therapy with EGFR-TKIs is a typical clinical approach [54]. A wide variety of lncRNAs have been found that influence how susceptible tumor cells to EGFR-TKIs. Numerous long noncoding RNAs (lncRNAs) have been suggested as prognostic indicators of EGFR-targeted therapy sensitivity for cancer of lung cells [55].

Signaling Pathways Associated with EGFR-Targeted Treatment Sensitivity: Gefitinib and erlotinib, two EGFR-TKIs, are frequently used to treat advanced NSCLC. However, the results have demonstrated that lung tumors often become resistant to EGFRTKIs linked to downstream signaling pathways such as EGFR, PMAPK, P-Akt, PI3K/Akt, and Ras/Raf/MAPK, which have been demonstrated to assess the effectiveness of gefitinib in patients with advanced NSCLC [56]. One of the subsequent methods is predominantly used by lncRNAs to control the susceptibility of lung cancer cells to EGFR-TKIs: 1). The MAPK/ERK pathway; 2) The PI3K/AKT/mTOR pathway; 3) The STAT3 pathway; 4) The mitochondrial pathway; 5) The cell cycle progression; or 6) EMT. Downregulated E-cadherin, increased vimentin, and EMT-related transcription elements (including ZEB1 and Slug) are associated with the development of EMT in NSCLC. This increases the pulmonary tumor's ability to resist EGFRTKIs [57]. The report that lncRNA SNHG12 engages with miR-181a to cause EMT by upregulating Slug and triggering the MAPK pathway while lowering caspase-3,9 activity inhibits the mitochondrial pathway.

Elevated SNHG12 lung cancer cells are resistant to gefitinib. It has been demonstrated that MIR31HG upregulates Mdm-2, activates the MAPK/ERK and PI3K/AKT pathways of signaling, and decreases the expression of the gene that suppresses tumors P53. It can therefore suppress the mitochondrial pathway and promote the advancement of the cell cycle. Consequently, MIR31HG contributes to reducing lung cancer cells' susceptibility to gefitinib [58]. It has been demonstrated that LncRNA UCA1 stimulates the AKT/mTOR, STAT3/MAPK/ERK, and EMT pathways of signaling in cells with lung cancer to promote gefitinib-acquired resistance and EMT. One of the scientist reported that LINC00665's association with Enhancer of Zeste homolog 2 (EZH2) and stimulation of the PI3K/AKT signaling pathway reduced the sensitivity of lung cancer cells to gefitinib. Feng *et al.* discovered that lncRNA MALAT1 improves EMT-mediated gefitinib resistance via the miR-200a/ZEB1 axis [59]. One of the scientist showed that the lncRNA human uterine and ovarian cancer-specific transcript 2 (HOST2) functions as a ceRNA to suppress miR-621 and increase the expression of the cellular cycle-associated protein. SYF2As a result, the cell cycle progressed and lung cancer cells were less susceptible to gefitinib [60].

LncRNAs as Lung Cancer Diagnostic Markers: Preclinical detection and treatment of lung cancer patients can halt the tumor's development. LDCT-based diagnostic imaging tests are widely used in the early identification of pulmonary carcinoma. It is still not ideal, though, because of its elevated fake positives percentage, which might occasionally cause radiologists to confuse malignant nodules for benign NCN. This can cause individuals who were misdiagnosed to undergo needless, intrusive tests later on [61]. Blood-based biomarker-based detection has the benefit of being noninvasive and can be used as a supplementary technique to LDCT for early lung cancer screening. There are differences in the molecular markers often employed to classify different histological subtypes. Progastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) are frequently employed as cancer indicators of small cell lung cancer (SCLC). NSCLC cancer indicators include carcinoembryonic antigen, cytokeratin 19 fragments (CYFRA 21-1), and squamous cancer cell antigen (SCCA) [62].

Histological analysis, however, is not very specific and is by nature objective. Certain tumor markers, like CEA, for instance, can be high not just in non-carcinogenic illnesses or benign tumors but also in LC [63]. It is consequently essential to find novel, sensitive, and reliable biomarkers to identify lung cancer early on. Numerous research have demonstrated that long noncoding RNAs (lncRNAs) are novel and potential molecular indicators for lung cancer detection, notably othermalignancy indicators based on blood, MALAT1 is one of the lncRNAs that is not especially accurate in identifying lung cancer. That is because different forms of cancer have abnormal MALAT1 activity [64].

Weber *et al.*'s research showed that MALAT1's sensitivity for NSCLC screening is only 56%. The sensitivity of MALAT1 for the glandular subtype LAD of NSCLC is significantly lower, at 48%. Early-stage lung cancer cannot be diagnosed with MALAT1 alone [65]. One may mitigate the disadvantage of a blood-derived molecular indicator that is cannot be very sensitive by selecting many molecular markers to be examined simultaneously in a panel. The performance of diagnosis can be enhanced by the supplementary use of molecular markers in a panel [66]. Utilizing CYFRA21-1, non-coding RNA SOX2OT, antisense noncoding RNA in the INK4 gene (ANRIL), CEA, and SCCA, an examination or diagnostic panel for non-small cell lung carcinoma was constructed. A logistic regression approach showed that the panel performed better than any single biomarker in terms of accuracy (79.2%) and empathy (77.1%). Additionally, this panel's accuracy (70.0%) and empathy (91.0%) were significantly higher then single molecular marker clinical efficacy in an autonomous verification set made up of clinical data [67].

Because cancer-derived long non-coding RNAs often develop a very stable secondary structure that is resistant to ribonuclease enzyme activity and persistent in peripheral circulation when present in sufficient quantities, they are suitable for quantitative detection. Blood-borne lncRNAs are employed in tumor early detection and serve as recently created tumor-specific molecular markers [68]. In statistics, the relationship between sensitivity and specificity in a test for illness is depicted by the receiver operating characteristic curve. The region in the curve can be used to determine diagnostic precision when assessing the utility of lncRNAs as a clinical indicator. AUC has a range of 0 to infinity and is expressed as a percentage. Higher AUC values indicate that the test has a higher level of diagnostic precision [69].

It can be problematic for patients' future care when lung cancer is misdiagnosed as a benign lung illness (like pneumonia) when it is discovered clinically. Certain lncRNAs are useful in differentiating between benign lung disease and pulmonary carcinoma [70]. Recent research has shown that Linc00152 can be used as a diagnostic indicator to distinguish between non-small cell lung carcinoma and mild lung disorders shown in **Fig. 3**. With this type of assay, the AUC value in a cohort was found to be 0.742 [71]. Similar findings were made by Jiang *et al.*, who discovered that lung cancer patients whole blood included elevated expression of the lncRNA XLOC_009167. This group's reported AUC value was 0.7005, which suggests that the diagnostic test has a moderately good level of accuracy. According to reports, lncRNA XLOC_009167 has a sensitivity of up to 90.1% for distinguishing between lung cancer and

pneumonia, which is in line with the significant specificity of genetic testing [72]. The fact that whole blood does not need serum or plasma to be separated simplifies clinical trials of this type and may spare certain sick individuals from painful diagnostic procedures if no cancer is discovered. In addition to lung cancer, several studies have demonstrated that lncRNAs can be used for other cancer diagnoses [73].

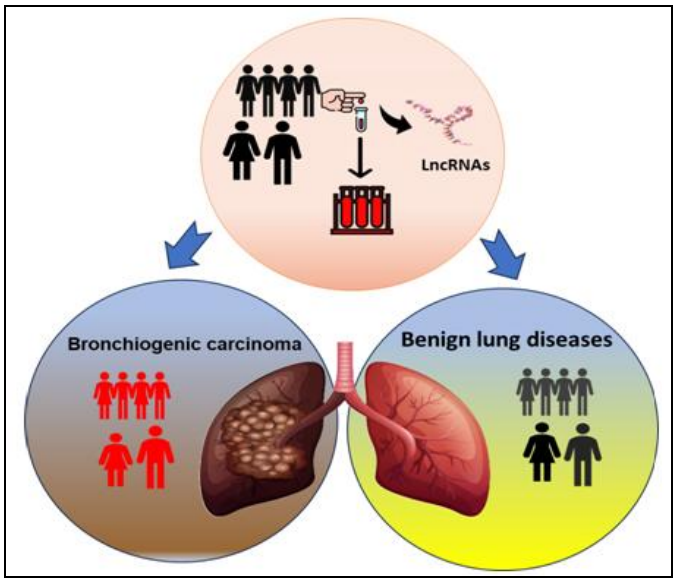

FIG. 3: LNCRNAs ARE A DIAGNOSTIC TOOL FOR EARLY SCREENING OF LUNG CANCER

LncRNAs as LC Prognostic Indicators: Patients with lung cancer are directly correlated with the therapy they receive and the rise in survival rate. The most frequent subtype, non-small cell lung carcinoma, has an incredibly low 5-decade comparative mortality rate. The poor prognosis associated with distant tumor metastases and lymph node metastases frequently complicates clinical patients [74]. For non-small cell lung carcinoma, the tumor node metastasis (TNM) staging system has shown to be a useful tool for prognostic estimation; nevertheless, its accuracy in this regard is limited [75]. Reputable and well-established statistical techniques including univariate and multivariate analysis are used to assess whether a long noncoding RNA (lncRNA) could be used as an autonomous cancer indicator for prognosticating lung tumor patients [76]. In lung cancer, a few lncRNAs have also been found to function as independent prognostic indicators. Therefore, it is plausible that repeated assessments of lncRNAs linked to prognosis could be used to quantify each patient's response to treatment [77].

Micro RNA (miRNA) and Lung Cancer: MiRNAs control how NSCLC metastasizes. The most prevalent endogenous short noncoding RNAs (ncRNAs) are called miRNAs, and they are expressed abnormally in a broad spectrum of human cancer kinds. The majority of microRNA genes are located inside the genomic areas that are linked to or sensitive to cancer, as several studies have shown [78].

It is believed that the etiology of many cancer types, including lung cancer, involves the epigenetic regulation of microRNA genes through DNA methylation or histone modification. Tumorigenesis and tumor formation are triggered by abnormal methylation of CpG sites inside promoter regions, which inhibits the production of tumor suppressor genes. In this case, it has been shown that the silencing of the miR-589-5p promoter by hypermethylation causes histone deacetylase 5 (HDAC5) to be overexpressed, which accelerates the growth and aggressiveness of NSCLC. Moreover, recent studies have shown that miR-493 inactivation caused by CpG hypermethylation enhances LC cell lines' apoptosis and tolerance to cisplatin [79].

Genome sequencing study indicates that miRNAs contribute to the development of lung cancer tumors from the very beginning to the end of their growth. miRNAs can act as tumor suppressors or oncogenic regulators, which is why they have been connected to a variety of malignancies. By attaching to mRNAs that encode oncoproteins and/or blocking the translation of oncogenic mRNAs, tumor suppressor miRNAs might potentially stop the proliferation of tumor cells. For example, it has been noted that non-small-cell lung adenocarcinoma has downregulated microR-320a, microR-584-5p, microR-144-5p, microR-613, and microR-582-5p (80). By altering the expression of mutant p53, microR-223-3p inhibits the migration and proliferation of lung squamous cell carcinoma cells, and miR-150-5p has been identified as a possible biomarker for predicting the advancement and recurrence of NSCLC. OncomiRs, another name for oncogenic miRNAs, are increased in cancerous cells and prevent cancer-fighting gene-encoding mRNAs from being translated. Examples of these genes include microR-141 in SCLC and microR-224, microR-301a/b, microR-130b,

microR-182-5p, and microR-20a in NSCLC. These oncomiRs play disproportionately large roles in the development and spread of cancer. To diagnose NSCLC patients, Results from comparing high serum miR-629 activity to conventional biomarkers could be more precise [81]. Furthermore, it is possible to halt the spread of cancerous cells by changing the way vital genes like MMP9, CXCR4, and E2F1 are expressed. Studies have shown that NSCLC cells that express high amounts of miR-152 have a decreased propensity to grow, divide, and spread by modulating the TNS1/Akt/mTOR/RhoA pathway.

A multitude of research works has hypothesized that miRNAs, including miR-32-5p in LAD and miR-574 5p in SCLC, influence carcinogenesis via the epithelial-mesenchymal transition (EMT), a biological mechanism associated with cancer's stemness, invasion, initiation, and resistance to therapy. MiRNAs have been shown to have a substantial impact on the regulation of genes engaged in both intrinsic as well as external pathways, including those that promote and inhibit apoptosis. In NSCLC tissues and cell lines, it was found that overexpression of miR-34b-3p triggers apoptosis, which is brought on by CDK4 knockdown. Furthermore, the up-regulation of microR-342-3p and microR-365b-3p can promote the death of NSCLC cells by selectively targeting serine/threonine-protein phosphatase 5 (PPP5C) and B-cell lymphoma 2 (BCL-2), respectively [82].

By targeting sirtuin 1 (SIRT1) and deactivating the SIRT1-mediated AMPK/mTORsignaling cascade, microRNA-217 mimics have also been shown to accelerate apoptosis in H1299 and A549 NSCLC cells. By controlling IMPs and hepatocyte nuclear factor 4 gamma (HNF4G) under hypoxic settings, miRNAs like miR-320b can also regulate the angiogenesis of lung cancers. Moreover, decreased microR-20a-5p activity stimulates cancer growth as well as angiogenesis by allowing the increased activity of RRM2, the ribonucleotide reductase regulatory component M2 in non-small-cell lung cancer cells. Specifically, microRNAs control how endothelial cells behave or how proteins that either promote or prevent the development of new blood vessels express themselves. As a result, changes in miRNA activity during cancer development provided evidence that miRNAs could be used as biomarkers for cancer diagnosis, prognosis, and treatment [83].

MiRNAs in LC Drug Resistant: Drug resistance persisted even after a range of therapeutic modalities, including radiation, chemotherapy, and targeted therapy, and posed a serious obstacle to the successful treatment of SCLC and NSCLC. Platinum is advised in conjunction with third-generation chemotherapeutic agents for the majority of patients with metastatic carcinoma of the lung; nevertheless, due to the disease's biology and clinical heterogeneity, the results are usually insufficient.

Recent studies have linked LC chemoresistance to several signaling pathways, including Wnt, PI3K/PKB/mTOR, mitogen-activated protein kinase (MAPK)/Slug, and MDM2/p53 signaling [84]. Moreover, miRNAs may affect the activity of viral proteins linked to drug resistance, including those controlling cellular division, DNA repair, and apoptosis. Radiation and chemotherapy resistance may arise due to any alteration in the control of miRNA, which might impact the above-described processes. LC cells employed distinct signaling pathways to impose miRNA-mediated resistance to drugs.

To make LC cells resistant to chemotherapeutic medication, for instance, miR-1269b and miR-103a-3p modulate the PTEN/PI3K/PKB and ER kinase pathways, accordingly, in response to cisplatin Current research has shown that certain microRNAs regulate EMT to affect LC drug resistance. MiR-27b, which targets the oncogene Snail1, has decreased EMT and increased lung tumor cell sensitivity to cisplatin. However, miR-410 overexpression in non-small-cell lung cancer supports epithelial-mesenchymal transition (EMT), which activates the PTEN/PI3K/mTOR axis and significantly enhances radioresistance [85]. To develop chemo-resistance, LC cells may also alter DNA damage repair pathways, like homologous recombination (HR), controlled by miRNAs. It has recently been found that the reduction of the nuclear enzyme poly ADP-ribose polymerase 1 (PARP1) by miR-7-5p may interfere with the process of doxorubicin-induced HR repair in dox-resistant SCLC cells, making them more susceptible to therapy. EGFR-TKIs have become

accessible in the recent few decades to treat individuals with lung cancer who also contain abnormalities in EGFR, including T790M and C797S. EGFR-TKIs are tiny medications that bind to the EGFR tyrosine kinase cytoplasmic region and stop autophosphorylation, which triggers the receptor and sends signals (86). Besides regulating the medical reaction, microRNAs are also shown to collaborate with chemotherapeutic agents. For instance, it was looked into whether NSCLC cells A549 and NCI-H441 could be more susceptible to cisplatin treatment if miR-202 expression was restored, which is regulated by the Ras/MAPK pathway. These results suggest that miRNAs may act as therapeutic agents by increasing the susceptibility of LC cells to chemotherapeutic treatments and chemoresistance indicators [87].

MicroRNA as an LC Biomarker: Several research studies have been carried out in an attempt to determine the most effective micro RNA-based benign technique for pulmonary carcinoma diagnosis and growth. Many miRNA biomarkers that have been confirmed in clinical studies and have been linked to the course and staging of LC were previously compiled by Landi *et al.* All biological components, including miRNAs, are strictly regulated to maintain physiological homeostasis. A group of ncRNAs known as circular RNAs (Cirhass) has been identified and their significant function has been confirmed by recently resurrected studies on other nonconventional RNA transcripts. More significantly, it has been discovered that these circRNAs affect the production and functionality of miRNA [88].

CONCLUSION: Non-coding RNAs are associated with regulatory elements in different types of cells. Their mechanism of action could have positive or negative effects in terms of their regulatory behavior. Likewise, a lot many ncRNAs control the functioning of lung tissues thereby modulating the overall functioning of lungs. These ncRNAs can be seen as potential targets in controlling various lung infections, especially lung cancer. The precise upregulation and downregulation of target ncRNAs can lead to desirable results for combating lung cancer in the human population. Still, a lot of ncRNAs need to be discovered for understanding their regulatory behaviour in regulating lung cancer. But even after the finding of target ncRNAs, the mode of controlling its expression via gene targeting in a human being is a great challenge in front of scientific community. However, the research of ncRNAs in the wider context of cancer of the lungs greatly helps our understanding of the progression of the disease and may soon make them a viable target for therapeutic medications.

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