

Review

Repertoires of MicroRNA-30 family as gate-keepers in lung cancer

Shruthi Kanthaje¹, Nandakishore Baikunje², Irfan Kandal³, Chandrabhas Koumar Ratnacaram^{1,*}

¹Yenepoya Research Centre, Yenepoya (Deemed to be University), University Road, Deralakatte, Mangalore, 575018 Karnataka, India

²Department of Pulmonary Medicine, K S Hegde Medical Academy, Nitte (Deemed to be University), Deralakatte, Mangaluru, 575018 Karnataka, India

³Department of Pulmonary Medicine, Yenepoya (Deemed to be University), University Road, Deralakatte, Mangalore, 575018 Karnataka, India

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1. Abstract

Lung cancer is a prominent global health issue responsible for the highest fraction of cancer-related mortality. The disease burden has incited the investigation of associated molecular pathways, to explore better therapeutic possibilities. MicroRNAs are extensively studied in recent years for their pivotal role in the regulation of several tumorigenic pathways. MicroRNA-30 (miR-30) family is primarily investigated in case of non-small cell lung cancer (NSCLC) and has been found to play the role of a tumour suppressor. There are six members of miR-30 family: miR-30a, miR-30b, miR-30c-1, miR-30c-2, miR-30d and miR-30e. They regulate several imperative signalling pathways like p53, PI3K/AKT, resulting in the modulation of key carcinogenic events involving cell proliferation, apoptosis, metastasis, epithelial-mesenchymal transition, and drug re-

sistance. Their altered levels are documented in NSCLC tissue and blood samples. They are suggested as biomarkers of disease progression and therapeutic outcomes in lung cancer. They possess immense therapeutic potential in the treatment of lung cancer and combat the emerging problem of drug resistance by modulating prime regulatory axes. However, there are many limitations in the existing studies, and additional research is required for the comprehensive understanding of pathways so that the tumour suppressive potential of miR-30 can be translated into clinical benefits. In this review, we present a deeper understanding of the regulatory role and clinical significance of miR-30 and have emphasized the emerging roles in lung cancer.

2. Introduction

Lung cancer is the most frequently diagnosed neoplasm, with 2.09 million new cases diagnosed in the year 2018 [1]. Even though the recent statistics by Siegel *et al.* [2] suggests that the death rates associated with lung cancer have decreased, mortality has increased over the years, from 1.59 million deaths in 2012 [3] to 1.76 million in 2018 [1]. Tobacco cigarette smoking (active and passive) is the principal risk factor, with exposure to air pollution, occupational exposure to asbestos, radon, metals, radiation therapy, human immunodeficiency virus (HIV) infection, alcohol consumption, and genetic susceptibility including epigenetics being other causal factors [4, 5]. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main types of lung cancer with NSCLC being the most common. Histologically, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are the major subtypes of NSCLC. Additionally, the presence of specific DNA mutations (*EGFR*, *ALK* and *ROS1*) allow further molecular classification.

Early-stage detection of NSCLC offers surgical resection as a treatment with most favourable prognosis, and survival rates can reach up to 90% [6]. However, the disease is asymptomatic and is often diagnosed at later stages (stage III/IV) making it difficult to offer any kind of curative treatments with survival rates sinking up to 15% [7]. Treatment modules include surgery, radiation therapy, interventional pulmonology and chemotherapy or a combination of the same. Besides these, immunotherapy seems promising, such as PD-1/PD-L1 inhibitors which include Nivolumab. Pembrolizumab (Keytruda) targeting PD-1 and Atezolizumab (Tecentriq) targeting PD-L1 [6]. The IV stage of lung carcinoma metastasizes to distant organs that include brain, bones, and adrenal glands. High-grade squamous cell and adenocarcinomas have exhibited overexpression of certain genes that include high smooth muscle actin (ACTA), c-MET and focal adhesion kinase (FAK) that regulate type 1 matrix metalloprotease (MMP14) [8].

MicroRNAs (miRNAs) are small RNA molecules which can regulate several target genes, thus regulating complex regulatory pathways. Role of miRNAs is evident in health and disease as observed by growing number of reports [9, 10]. Many miRNAs like miR-21, miR-30, miR-34, miR-210 etc. are studied for their role in carcinogenesis, diagnosis, prognosis, and therapeutic potential in lung cancer [11]. Most importantly, several studies have shown a significant downregulation and tumour suppressive potential of miR-30 family members in lung cancer [12–14]. This review discusses an extensive overview of the current research on the role of miRNAs in lung cancer with a major focus on miR-30 family.

3. MicroRNAs

MicroRNAs (miRNAs) are endogenous, highly conserved, small non-coding RNA molecules involved in the regulation of gene expression [15, 16]. Mature miRNAs are single-stranded RNAs containing 18–25 nucleotides, which are the end products of processed primary and precursor miRNAs [17]. Approximately 1000 nucleotide long primary miRNA (Pri-miRNA) is processed using the microprocessor complex to produce 70 nucleotide long stem-looped precursor miRNA (pre-miRNA) in the nucleus. This pre-miRNA is transported to the cytoplasm using Exportin-5 and processed to mature single stranded miRNA using DICER [18]. With the advent of high throughput techniques, an increasing number of miRNAs are being sequenced. The latest miRBase registers 48,860 mature miRNA sequences from 271 organisms, and human genome encodes for 2,654 of them [19].

Duplex miRNA is loaded on to Argonaute along with other associated proteins comprising the RNA induced silencing complex (RISC). Argonaute proteins form the fundamental component of RISC performing endonucleolytic cleavage of target mRNA based on the guide (miRNA) and target strand (3' UTR of mRNA) complementarity, resulting in gene silencing. Repression of gene expression can also result from translational inhibition if miRNA-mRNA possesses partial complementarity [15, 20]. The canonical pathway for miRNA biogenesis [18] and its mechanism of target inhibition is described in Fig. 1.

Different miRNAs are assembled into families indicating a derivation from a common ancestor. The miRNA family also hint towards similar sequence, secondary structure, and/or shared biological function [16]. Sister miRNAs of the family mostly share conserved seed sequence resulting in the silence of common target genes and hence shared regulatory role. Nevertheless, recent evidence suggests that complementarity may extend beyond seed region (3' end of miRNA) resulting in diverse target profiles for the miRNAs of the same family [21].

Post-transcriptional crosstalk between miRNA and mRNA results in the complex regulation network leading to minimization of transcriptional noise, maintenance of threshold protein or mRNA levels, and/or acting as switch-like repression [22, 23]. These attributes of miRNA have made it relevant in most physiological and pathological conditions, including cancer [24]. The genomic locations of more than half of the miRNA population are at fragile sites signifying its relevance in cancer [25]. The deregulated expression levels of various miRNAs in several cancers have been documented, and they may act as either oncogenes or tumour suppressors depending upon their targets [26]. Also, some miRNAs do possess tissue specificity substantiating their regulatory role in differentiation status and tissue identity, as well as its therapeutic potential [27].

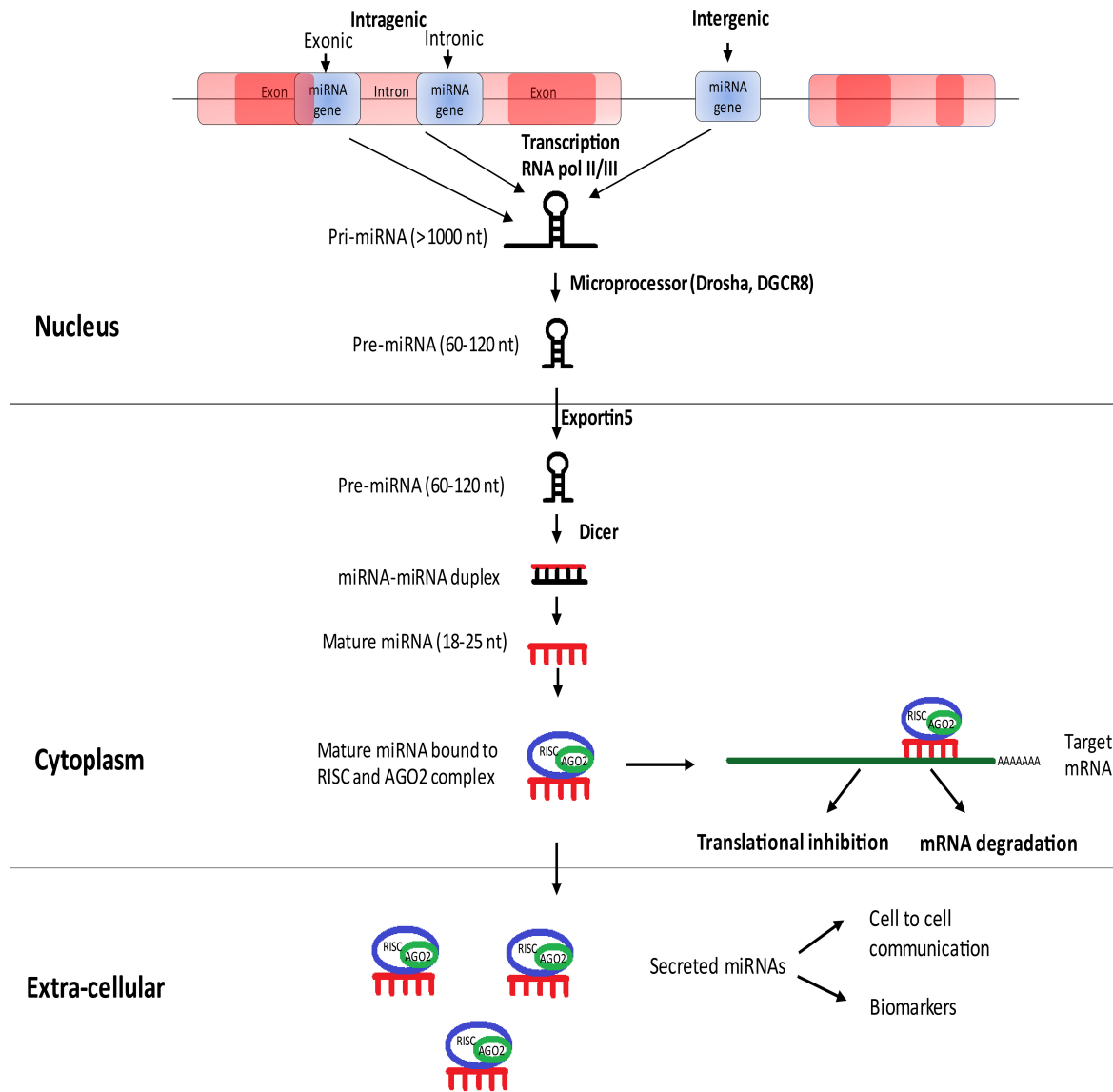


Fig. 1. Canonical pathway for miRNA biogenesis.

as described in Fig. 2. Additionally, many miRNAs are investigated for their specific role in drug resistance [28] and metastasis [29].

miR-21 is a putative oncogene that functions as an anti-apoptotic factor which is the most studied miRNA in the context of cancer. It is found to be overexpressed in breast cancer, colorectal cancer, neuroblastoma, lung cancer, hepatocellular carcinoma (HCC), pancreatic cancer, glioblastoma, leukaemia and lymphoma [30] which can serve as a therapeutic target. Clinical trials using anti-miR-21 oligonucleotides have shown to reduce reactive oxygen species (ROS) thus decreased tumour size [24]. Similarly, miR-17-92 cluster is often studied for its oncogenic role in several cancers, and it is said to influence, cell proliferation, angiogenesis, and metastasis. Moreover, the targets of this cluster include phosphatase and tensin homologue deleted on chromosome 10 (*PTEN*) and E2 family

of transcription factors. Overexpression of this cluster inhibits *PTEN*, thereby phosphorylation of *AKT* leading to, cell proliferation, angiogenesis and metastasis [31]. Further, miR-122 is frequently studied liver-specific miRNA, in case of HCC by targeting *ADAM10*, *SRF*, *IGF1R* [32], and *FOX* family genes besides its regular role in homeostasis and metabolism [33]. Additionally, miR-34 is a well-known tumour suppressor miRNA and is shown to inhibit carcinogenesis via regulating *TP53*. MRX34, the miR-34a mimic, is a first tumour-targeting miRNA to get into clinical trials for the treatment of several solid tumours including, HCC, renal cell carcinoma (RCC), lung cancer, melanoma etc. [34, 35]. Similarly, several circulating miRNAs individually and as a signature profile are explored for their biomarker potential in the diagnosis and prognosis of cancer [36].

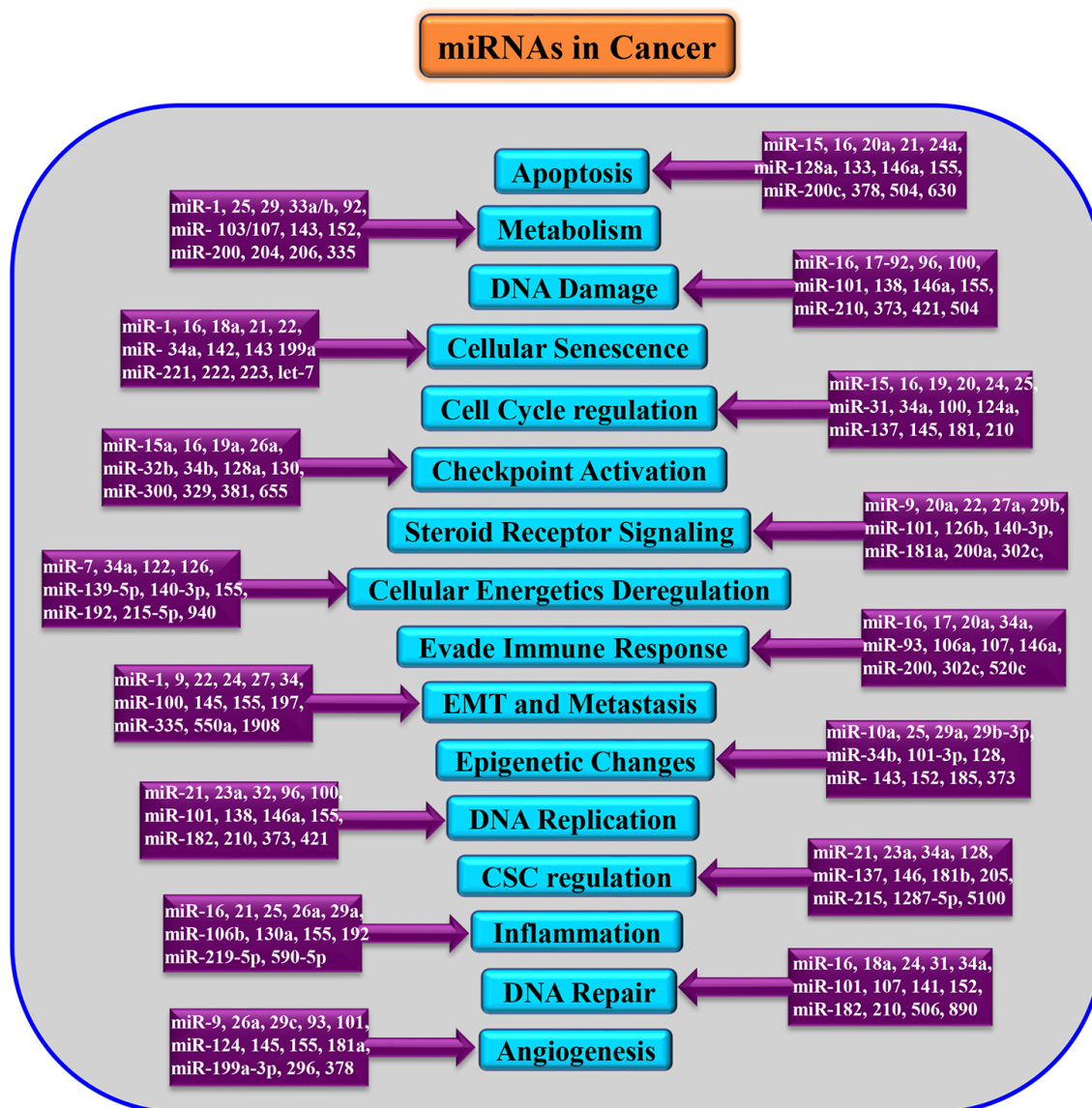


Fig. 2. Dysregulation of miRNAs in various cancers. EMT, Epithelial-Mesenchymal Transition; CSC, Cancer Stem cells.

In lung cancer, many miRNAs are investigated to understand their role in the process of tumorigenesis and to evaluate their biomarker potential [37]. miR-150 is demonstrated to promote metastasis in primary lung cancer by targeting *FOXO4*. It is also proved to be involved in the proliferation of A549 cell lines through p53 mediated mechanism as it harbours miR-150 binding site [38]. Meanwhile, a decreased expression of miR-145 is observed in NSCLC tissues. Grouped under a tumour suppressor, it inhibits cell migration and invasion by silencing *RIOK2* and *NOB1*. It is usually downregulated in many cancers and is shown to be involved in cell cycle regulation. This miRNA is considered to be a therapeutic target for the management of lung cancer [31]. miR-486 may act as a potential therapeutic target in NSCLC by regulating PI3K/AKT pathway [39]. Another study has shown its high diagnostic and prognostic accuracy from the meta-analysis of different cancers

as described in Fig. 3. Moreover, the circulating miR-486 had higher diagnostic value compared to the direct specimen that substantiates its value as a biomarker [40].

Similarly, the miR-200 family and miR-183~96~182 cluster are downregulated in lung cancer and are involved in suppressing metastasis. Two of the targets for the cluster is *FOX2* and *ZEB1* whose expression triggers EMT, migration and metastasis [41, 42]. Furthermore, single nucleotide polymorphism (SNP) variant in miR-196a2 and miR-146a exhibited enhanced risk for lung cancer in North Indian population [43]. miR-30 family is one of the widely studied miRNAs in lung cancer, and here we highlight their physiological role, upstream regulation, downstream targets, functional role and clinical significance in lung cancer.

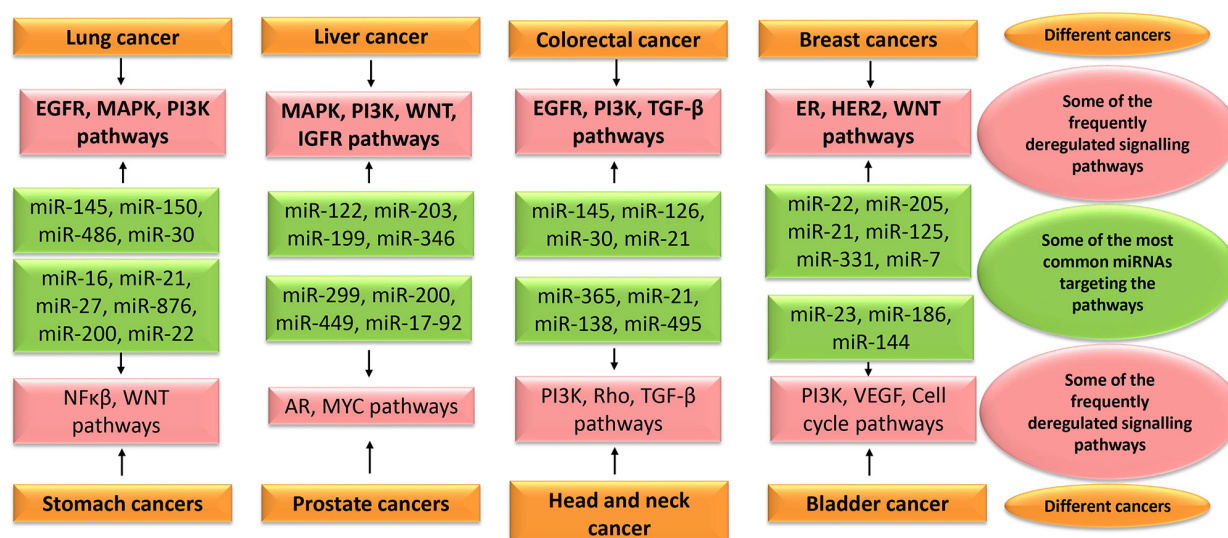


Fig. 3. Some of the most common miRNAs targeting the frequently deregulated signalling pathways in various cancers. EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; PI3K, Phosphoinositide 3-kinase; IGFR, Insulin-like growth factor receptor; TGF, transforming growth factor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; AR, Androgen receptor; VEGF, Vascular endothelial growth factor.

Table 1. miR-30 family members, its chromosomal location, and sequence of mature miRNAs.

| S. No. | miRNA | Chromosome location of the gene | Mature miRNA sequence (with underlined seed sequence) |
|--------|-------------------|--|---|
| 1 | hsa-miR-30a-5p | 6q13 (71403551..71403621, '–'ve strand) | <u>UGUAAACA</u> UCCUCGACUGGAAG |
| 2 | hsa-miR-30b-5p | 8q24.22 (134800520..134800607, '–'ve strand) | <u>UGUAAACA</u> UCCUACACUCAGCU |
| 3 | hsa-miR-30c-1-5p | 1p34.2 (40757284..40757372, '+'ve strand) | <u>UGUAAACA</u> UCCUACACUCUCAGC |
| 4 | hsa-miR-30c-2-5p | 6q13 (71376960..71377031, '–'ve strand) | <u>UGUAAACA</u> UCCUACACUCUCAGC |
| 5 | hsa-miR-30d-5p | 8q24.22 (134804876..134804945, '–'ve strand) | <u>UGUAAACA</u> UCCCGACUGGAAG |
| 6 | hsa-miR-30e-5p | 1p34.2 (40754355..40754446, '+'ve strand) | <u>UGUAAACA</u> UCCUUGACUGGAAG |
| 7 | hsa-miR-30a-3p* | 6q13 (71403551..71403621, '–'ve strand) | <u>UUUCAGU</u> CGGAUGUUUUCAGC |
| 8 | hsa-miR-30b-3p* | 8q24.22 (134800520..134800607, '–'ve strand) | <u>UGGGAGG</u> UGGAUGUUUACUUC |
| 9 | hsa-miR-30c-1-3p* | 1p34.2 (40757284..40757372, '+'ve strand) | <u>UGGGAGAG</u> GGUUGUUUACUCC |
| 10 | hsa-miR-30c-2-3p* | 6q13 (71376960..71377031, '–'ve strand) | <u>UGGGAGA</u> AAGCUGUUUACUCU |
| 11 | hsa-miR-30d-3p* | 8q24.22 (134804876..134804945, '–'ve strand) | <u>UUUCAGU</u> CAGAUGUUUUCUGC |
| 12 | hsa-miR-30e-3p* | 1p34.2 (40754355..40754446, '+'ve strand) | <u>UUUCAGU</u> CGGAUGUUUACAGC |

*Rare or inactive.

4. miR-30 family

The miR-30 is a broadly conserved miRNA family containing twelve mature miRNA members including miR-30a, miR-30b, miR-30c-1, miR-30c-2, miR-30d, and miR-30e, generated from both 5p and 3p arms of respective pre-miRNA [19, 44]. All mature miRNAs generated from the 5p arm of miR-30 family pre-miRNAs are active, and that from 3p are rare or inactive (3p*) [45]. miR-30c-1 and miR-30e are encoded by the genes located in the positive strand of Chromosome 1, while miR-30a and miR-30c-2, as well as miR-30d and miR-30b, are encoded by genes located in the negative strand of Chromosome 6 and 8 respectively [19] (Table 1). We found that only miR-30c-1 and miR-30e are intragenic miRNAs located in the intron region of Nuclear Transcription Factor Y Subunit Gamma (*NFYC*) gene using miRIAD database [46]. However, the association of

miR-30 and *NFYC* in lung cancer not explored so far. The 5p mature miRNAs have a conserved 8mer seed sequence of “GUAAACA”; however, 3p mature miRNAs have either UUUCAGU /UGGGAGG(A) [47].

There are limited studies related to the upstream regulation of miRNAs in physiology and diseases. Hypermethylation of the promoter region of miR-30 gene was observed in pancreatic cancer [48], breast cancer [49] and head and neck squamous cell carcinoma (HNSCC) [50] resulting in the downregulation of mature miRNA. Moreover, in HNSCC, copy number loss was also responsible for the decreased expression of miR-30 [50]. *SP1*, a transcription factor involved in energy metabolism, acts as an activator of miR-30c expression by binding to the promoter region [51]. Similarly, β -Catenin/TCF can also directly bind to the promoter region of miR-30a and activate its ex-

pression [52]. Only one mechanism of downstream regulation of miR-30b/c activity has been reported through target-directed miRNA degradation (TDMD) by *SERPINE1*, a serine protease inhibitor, in a study by Ghini *et al.* [53]. These studies suggest the existence of a sophisticated regulation network for the expression of miRNAs that needs to be explored further to understand their substantial therapeutic potential.

The role of miR-30 has been observed in various aspects of human physiology. Its expression in mammalian cells was first discovered in the HeLa cell line by Lagos-Quintana *et al.* [54], along with 21 other novel miRNAs. The sister miRNAs are involved in the regulation of various physiological signalling pathways, including osteogenic differentiation and development [55, 56], as well as animal reproductive development [57]. Besides, miR-30 was also shown to play a crucial role in lipogenesis and adipose differentiation [58]. miR-30b and miR-30c are involved in vascular development and angiogenesis [59]. They favour epithelial phenotype by silencing genes involved in mesenchymal transition [60]. These studies suggest the significance of miR-30 family in development and differentiation of various cell types. The prominent physiological involvement of miR-30 shows that their deregulation is involved in several pathological conditions, including cancer [61].

Although miR-30 has a prominent tumour repressing role in many cancers, few studies also have documented its oncogenic role in some of the cancers indicating its diversity of targets. Overexpression of miR-30 has been reported in many cancers by inhibiting *p53* and *p16INK4A* disrupting senescence in cells [62]. In breast cancer, it plays the role of tumour suppressor [63] by regulating several key signalling pathways like MAPK/KRAS [64], *p53* etc. [65]. miR-30 acts as a tumour suppressor in thyroid cancer and also helps in distinguishing anaplastic thyroid cancer and differentiated thyroid cancer [66]. Saleh *et al.* [50] showed that miR-30a/e could inhibit growth and tumorigenicity in HNSCC; they also revealed the therapeutic potential of miR-30a. However, it was reported by Saad *et al.* [67] that miR-30a is upregulated in case of alcohol-induced HNSCC resulting in pathogenesis and progression of cancer. In HCC, downregulated levels of miR-30e have been observed, and it is said to target JAK1/STAT3 pathway to restrain tumorigenesis. Similarly, miR-30a can inhibit proliferation, migration, and invasion in HCC by directly inhibiting *FOXAI* [68–70]. Xiong *et al.* [71] showed that miR-30b impedes epithelial-mesenchymal transition (EMT) and hinders oncogenicity in pancreatic cancer. However, an oncogenic role of miR-30a/b/c was also observed in pancreatic cancer and are involved in the regulation of drug resistance, migration, and invasion [72]. In gastric cancer, miR-30a is involved in decreasing multidrug resistance [73] and inhibits cell growth by regulating RAB31/GLI1 pathway [74]. In RCC, miR-30a and miR-30b are documented

to inhibit tumorigenesis, metastasis, and EMT by targeting *GRP78*, a crucial regulator of endoplasmic reticulum (ER) stress response, and *GNA13*, a member of G-protein family [75]. miR-30a acts as a tumour suppressor in melanoma by downregulating metastasis through regulating *SOX4* and *ZEB2* [76, 77]. miR-30d and miR-30e were associated with failure-free survival (FFS) in classical Hodgkin lymphoma (cHL). Additionally, miR-30d acts as an oncomiR and may also be involved in doxorubicin related chemoresistance in cHL [78]. Further, miR-30d serves as one of the prognostic markers for primary central nervous system lymphoma [79]. Hence, the literature suggests the diverse role of miR-30 family in various cancers by regulating an array of targets (Table 2, Ref. [59, 60, 62, 64, 67–78, 80]).

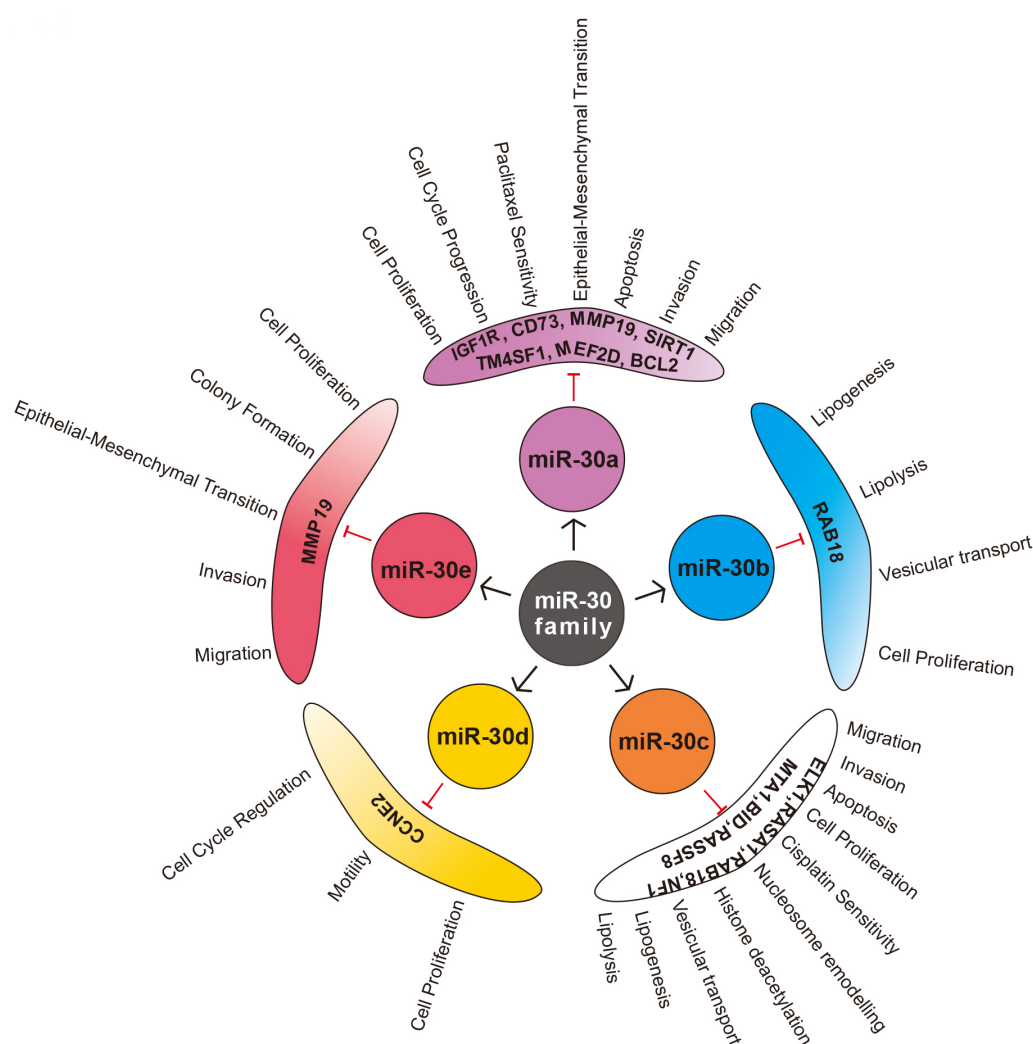
5. miR-30 and lung cancer

miR-30 family is one of the top five highest expressed miRNAs in normal adult human and mouse lung, suggesting the evolutionary conservation [81]. It is also one of the families found to be airway specific with higher expression in alveolar macrophages [82]. The role of miR-30 family is mostly studied in case of NSCLC (adenocarcinoma and squamous cell carcinoma), and only limited reports are available in case of large cell carcinoma, SCLC, and mesothelioma of lung. miR-30a is the most studied sister miRNA of miR-30 family, and maximum studies have observed lower expression of miR-30 family members in case of lung cancer tissue, blood, cell lines as well as in animal models, signifying its tumour suppressive role. Various studies have elucidated several targets and pathways through which these sister miRNAs regulate different steps of carcinogenesis (Fig. 4).

Smoking is the primary cause of lung cancer and cigarette smoke is also implicated in miRNA dysregulation. Although the exact mechanisms behind the abrogation of miRNA expression is unclear, the highly mutagenic oxidative compounds and free radicals generated by smoking are said to interact with the nucleotides. As most of the miRNA genes are located in fragile sites of the genome, they are more vulnerable [83, 84]. Even though the miR-30 family has not been investigated independently in relation to smoking, several studies have observed its association, along with other miRNAs. miR-30 family is one of the most prominently downregulated miRNA families in lung tissues of Sprague-Dawley rats exposed to environmental cigarette smoke for four weeks (miR-30a/c; >3 fold) [85]. However, miR-30b/c were found to be upregulated significantly in the plasma of smokers as compared to non-smokers. The same study also observed that miR-30b/c/d were downregulated in subjects who quit smoking as compared to smokers [86]. In another study, miR-30d was found to be associated with survival of lung adenocarcinoma patients with current smoking habits [87]. miR-30c is also shown to play a key role in emphysema [84]. However, according to a study

Table 2. Role of miR-30 family members in cancers other than lung cancer.

| S. No. | Type of cancer | miR-30 family members | Role | Reference |
|--------|--------------------------|-----------------------|------------------|--------------|
| 1 | Breast Cancer | miR-30a/c/e | Tumor suppressor | [59, 60, 62] |
| 2 | Thyroid cancer | miR-30a/b/c/d/e | Tumor suppressor | [64] |
| 3 | Head and neck cancer | miR-30a/b/c/d/e | Tumor suppressor | [43] |
| 4 | Hepatocellular carcinoma | miR-30a | Oncogenic | [66] |
| 5 | Pancreatic cancer | miR-30a/b/c | Tumor suppressor | [71] |
| 6 | Gastric cancer | miR-30a/c-2 | Tumor suppressor | [72, 73, 80] |
| 7 | Renal cell carcinoma | miR-30a/b | Tumor suppressor | [74, 75] |
| 8 | Melanoma | miR-30a | Tumor suppressor | [76, 77] |
| 9 | Lymphoma | miR-30d/e | Oncogenic | [78] |

**Fig. 4. Sister miRNAs of miR-30 family, its validated targets and functional significance in Non-small cell lung cancer (NSCLC).**

performed by Seike *et al.* [88], it is also downregulated in lung cancer tissues as compared to normal lung tissues, in case of never smokers. These conflicting outcomes indicate that association of miR-30 with smoking status is not entirely clear, and more studies are required to comprehend its role in the same.

Many studies have suggested its association with several clinical parameters of lung cancer by observing its varied levels in human serum, plasma and/or tissue (Table 3, Ref. [88–105]). Functionally, miR-30 family regulates chief pathways involved in NSCLC which are discussed below in detail.

Table 3. Association of miR-30 family deregulation with various clinical parameters as indicated by several studies.

| Parameters | | miRNA | Levels | Reference |
|---------------------------------|------------------------------|---|--------|----------------------|
| NSCLC sample (cancer vs normal) | Tissue | miR-30a-3p/5p, miR-30b, miR-30c, miR-30d, miR-30e-3p/5p | ↓ | [88–96, 98, 100–104] |
| | Plasma | miR-30e-3p/5p | ↓ | [102] |
| | Serum | miR-30a and miR-30e-3p | ↑ | [94] |
| Age (elderly vs young) | | miR-30a | ↑ | [93] |
| Gender (female vs male) | | miR-30d | ↑ | [103] |
| | | miR-30a | ↓ | [88, 93] |
| Stage (advanced vs initial) | | miR-30e-3p | ↑ | [105] |
| | | | ↓ | [94] |
| Metastasis (yes vs no) | | miR-30a/d/e-3p | ↓ | [93, 103, 105] |
| Dedifferentiation (yes vs no) | | miR-30e | ↓ | [94] |
| Tumor Size (high vs low) | | miR-30a and miR-30e-3p | ↓ | [93, 94] |
| Survival | OS (↑) | miR-30a, miR-30c, miR-30e | ↑ | [89, 99, 102] |
| | PFS (↑) | miR-30a, miR-30c, miR-30e-3p/5p | ↑ | [89, 99, 102, 105] |
| Prognosis (poor) | | miR-30d/a | ↓ | [88, 103] |
| Drug Response | Erlotinib (PFS ↑) | miR-30b/c | ↓ | [99] |
| | Paclitaxel (DFS ↓ and No RR) | miR-30a | ↓ | [97] |

OS, Overall survival; PFS, Progression free survival; DFS, Disease free survival; ↑, upregulation; ↓, Down regulation.

5.1 Role of miR-30 in proliferation, cell cycle regulation and apoptosis

miR-30 family can regulate proliferation, cell cycle and apoptosis through various pathways to inhibit tumorigenesis in NSCLC. Guan *et al.* [14] showed that miR-30a could directly target *SIRT1*, a NAD-dependent deacetylase to suppress lung cancer. miR-30a mimics inhibited the expression of *SIRT1*, while miR-30a inhibitors produced the opposite effect. *SIRT1* can deacetylate *p53*, preventing its downstream transcriptional activity and apoptosis [89]. Interestingly, *p53* can bind to miR-30a promoter and transcriptionally activate the same [65]. Clinical samples of NSCLC show low *p53* acetylation, lower levels of miR-30a and upregulation of *SIRT1* expression [14, 90] suggesting an active loop of miR-30a/*SIRT1*/*p53* in tumorigenesis. Further, miR-30 mimics can also target *MEF2D*, a prominent transcription factor regulating cell proliferation and apoptosis [12]. Evidence suggests that *MEF2D* is highest expressed in NSCLC patients with COPD compared to NSCLC patients without COPD and COPD patients without NSCLC [91]. These observations indicate *MEF2D* may act as a mechanistic link between chronic inflammation and cancer development. As miR-30a regulates *MEF2D*, it would be interesting to understand its expression in COPD, which forms a significant risk factor for lung cancer. Additionally, miR-30b/c can inhibit *Rab18*, a Ras superfamily G protein to impede the cell proliferation in NSCLC [92]. *CCNE2*, a cyclin regulating cell cycle, driving the G1/S transition is a target of miR-30d [13]. The expression of *CCNE2* is profoundly increased in NSCLC patients suggesting that it acts as an oncogene [93]. Further, miR-30a can also directly target Insulin-like growth factor 1 recep-

tor (*IGF1R*) and regulate PI3K/AKT pathway by inhibiting several cell cycle regulators like *CDK2*, *CDK4*, *Cyclin A2*, *Cyclin D1*. The authors observed inhibition of cell proliferation, G1/S and S/G2 transition *in vitro* [94]. miR-30a also found to target *CCNE2* in prostate cancer [95] indicating that miR-30 family members may act as a regulator of the cell cycle to render its tumour suppressive functions.

5.2 Role of miR-30 in epithelial-mesenchymal transition (EMT)

Conversion of stationary epithelial cells to migratory mesenchymal cells by the process of epithelial-mesenchymal transition (EMT) is the hallmark of cancer metastasis [96]. miR-30 is demonstrated to regulate EMT in NSCLC under many studies. Matrix metalloproteases (MMP) are one of the main class of proteolytic enzymes involved in tumour invasion by enabling basement membrane penetration. Several members of MMPs (*MMP-1*, *MMP-2*, *MMP-7*, *MMP-9*, *MMP-12*, *MMP-13*, *MMP-19*, *MMP-26*) are found to be upregulated in lung cancer [97, 98]. Yu *et al.* [98] found a negative association between miR-30 and *MMP-19*, hinting that it might be a direct target. Moreover, miR-30 also found to downregulate the expression of *MMP-2* and *MMP-9* in prostate cancer [99]. Further, *CD73* is a cell surface enzyme which dephosphorylates extracellular AMP to adenosine, is significantly overexpressed in NSCLC cell lines and tissues [106]. It is said to modulate tumour immune response and promote growth and metastasis [107]. miR-30a mimics have been shown to inhibit proliferation and migration by directly regulate *CD73* in NSCLC [106] as well as colorectal cancer [100]. Metastasis associated protein 1 (*MTA1*), a promoter of EMT and metastasis is overexpressed in NSCLC as evidenced in var-

ious studies [101, 108, 109]. miR-30 can directly inhibit *MTA1* by binding to 3'-UTR, in hepatocellular carcinoma [102], gastric cancer [103] and NSCLC [108]. *NFIB* is another oncogenic transcription factor regulated by miR-30d to modulate migration and invasion in lung cancer [110]. miR-30a can also target predominant pro-metastatic protein of Eya family called *EYA2*, and inhibit migration as well as invasion [80]. miR-30a/c can regulate *TM4SF1*, a glycoprotein involved in the regulation of metastasis, cell proliferation and stemness [111]. In contrast, Kawaguchi *et al.* (2017) observed only slight increase in migration capacity of A549 cells transfected with miR-30a compared to controls and no change in any cellular properties like proliferation, cell cycle, drug sensitivity [104].

5.3 Role of miR-30 in drug resistance

Drug resistance is a prominent reason for therapeutic failure resulting in disease progression or recurrence in lung cancer. Treatment with paclitaxel (alone and in combination) is an approved therapy for advanced NSCLC [105]. Multiple studies have found the enhanced expression of anti-apoptotic protein BCL-2 in chemoresistance, including paclitaxel [112, 113]. Xu *et al.* [114] proved that *BCL2* is the direct target of miR-30a using mimics and anti-miRs. miR-30a can directly inhibit *BCL2* and enhance paclitaxel sensitivity by modulating apoptosis. A lower expression of miR-30a in cells indicate paclitaxel resistance. Additionally, *PI3K* is involved in the resistance mechanisms of several tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib, are also regulated by miR-30 [115]. *MET* (hepatocyte growth factor receptor tyrosine kinase) expression and phosphorylation is observed with primary and acquired resistance to EGFR TKI treatment. miR-30b/c, miR-221, and miR-222 were found to be regulated both by *EGFR* and *MET* and may have therapeutic benefits in overcoming drug resistance to TKIs [116]. miR-30c is also regulated in the upstream by wild type and mutant *KRAS* (*KRAS*^{G12D}), a proto-oncogene involved in modulation of sensitivity of different chemotherapeutic agents in NSCLC. miR-30c can directly inhibit several tumour suppressor genes like *NF1*, *BID*, *RASSF8*, and *RASA1*, and induce drug resistance [117]. The last two studies indicate an oncogenic function of miR-30, which seems to be especially active during drug resistance regulated by *EGFR*, *MET* or *KRAS* in the upstream.

5.4 Clinical significance

Several studies have compared the expression of sister miRNAs belonging to the miR-30 family in tissue and blood samples of NSCLC patients. These studies have used as low as five [92] to as high as 160 paired tissue samples [111]. Most of the studies observed a downregulated expression of miR-30a [12, 82, 111, 118, 119], miR-30b [92], miR-30c-1 [92, 108, 120], miR-30c-2 [121], miR-30d [98, 122–124], miR-30e [92, 98, 125] in NSCLC tissues

as compared to adjacent normal tissue samples, suggesting its major role as tumour suppressor miRNA. Only one study reported an elevated expression of miR-30c in tissue samples of NSCLC patients [117]. The paradoxical role of a single miRNA acting as both tumour suppressor and oncogene is observed in many studies as well [126, 127]. This observation may be attributed to the fact that a single miRNA can target many mRNAs which include both oncogenes and tumour suppressors. Additionally, single mRNA can be regulated by multiple miRNAs complicating the regulation process. Moreover, several other factors like the immune system, tumour microenvironment, infections, therapy sensitivity, and mutations may also affect the miRNA-mRNA interactions. The net effect of a miRNA as a tumour suppressor or oncogene depends on fine-tuning the balance between these interactions [128].

The altered miR-30 expression is correlated to several clinical parameters like the stage of the tumour [129], tumour size [111], lymph node metastasis and poor prognosis [123, 129], smoking status [122], and NSCLC dedifferentiation [118]. miR-30 downregulation is also associated with survival parameters like shorter overall survival (OS), progression-free survival (PFS) [111]. Interestingly, older patients showed higher expression of miR-30a [129]. The same miRNA is demonstrated as age-dependent miRNA that can impair keratinocyte differentiation and induce apoptosis in another study [130]. Also, expression of miR-30d was higher in females [123]. Its sister miRNA miR-30b is regulated by estrogen, indicating a hormonal control [131]. These observations highlight the importance of considering patient age and gender while comparing different studies. However, few studies found no correlation between altered miR-30 expression levels and any clinicopathological features of patients [82, 111, 122].

5.5 Biomarkers

The first evidence of miRNAs as biomarkers in cancer was recognized during 2008 in the serum of diffuse large B-cell lymphoma patients [132]. Since then, many miRNAs are examined for their biomarker potential in cancer [133]. Most of the studies involving miR-30e in lung cancer are from the perspective of the biomarker. Its altered expression was detected in three studies based on different array technology platforms [14, 118, 134]. Silva *et al.* [134] examined the levels of miR-30e-3p in more than 100 NSCLC patient's plasma vesicles and found it to be downregulated. The levels of the same were significantly upregulated in advanced stages of the tumour distinguishing the patients for their possibility of surgery. An enhanced level of miR-30e-3p was also associated with higher disease-free survival (DFS) rates. However, no association was observed with OS. Significant downregulation of miR-30e-5p was also observed in both tissue and plasma of 59 NSCLC patients. Although the tissue levels of miR-30e-5p did not correlate with any clinicopathological features, its circula-

Table 4. Targets of miR-30 family members validated by Luciferase reporter assay as listed in miRTarBase.

| S. No. | Target gene (Official Gene Symbol) | Gene function |
|--------|---------------------------------------|--|
| 1 | BDNF | Brain-derived neurotrophic factor; growth factor |
| 2 | NOTCH1 | NOTCH homolog 1; transmembrane receptor |
| 3 | BECN1 | Autophagy related gene |
| 4 | TNRC6A | Trinucleotide repeat containing adaptor 6A; involved in post-transcriptional gene silencing |
| 5 | MBNL1 | Muscleblind like splicing regulator 1; Splicing regulator |
| 6 | SMAD1 | Mothers against decapentaplegic homolog; signal transducers for receptors of the transforming growth factor beta |
| 7 | DTL | Denticleless E3 Ubiquitin Protein Ligase Homolog; polyubiquitination |
| 8 | SNAI1 | Zinc finger protein; transcription factor |
| 9 | PIK3CD | Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; phosphorylation |
| 10 | PRDM1 | PR domain zinc finger protein 1; repressor of beta-interferon gene expression |
| 11 | 7-Sep | Septin 7 |
| 12 | AVEN | Apoptosis and caspase activation inhibitor |
| 13 | FOXD1 | Forkhead box D1; transcription factors |
| 14 | ABL1 | ABL proto-oncogene 1; non-receptor tyrosine kinase |
| 15 | MTDH | Metadherin; involved in RNA-induced silencing complex |
| 16 | VIM | Vimentin; type III intermediate filament protein |
| 17 | RUNX2 | RUNX family transcription factor 2 |
| 18 | ERG | ETS-related gene; transcription factor oncogene |
| 19 | ESR2 | Estrogen Receptor 2; nuclear receptor transcription factors |
| 20 | BCL11A | B-cell lymphoma/leukemia 11A; zinc-finger protein |
| 21 | BCL9 | B-cell CLL/lymphoma 9; transcriptional co activator |
| 22 | HSPA5 | Heat shock protein family A (Hsp70) member 5; folding and assembly of proteins in the ER |
| 23 | EYA2 | EYA Transcriptional Coactivator And Phosphatase 2 |
| 24 | SOX4 | SRY-box transcription factor 4 |
| 25 | IL21R | Interleukin 21 receptor; type I cytokine receptors |
| 26 | UBE3C | Ubiquitin protein ligase E3C |
| 27 | CBX3 | Chromobox 3; chromobox 3 component of heterochromatin |
| 28 | TP53 | Tumor protein P53; tumor suppressor protein containing transcriptional activation |
| 29 | CD99 | CD99 Molecule (Xg Blood Group); cell surface glycoprotein |
| 30 | LOX | Lysyl oxidase |
| 31 | MBNL3 | Muscleblind like splicing regulator; egulation of alternative splicing |
| 32 | NCAM1 | Neural cell adhesion molecule 1; cell adhesion protein |
| 33 | MBNL2 | Muscleblind like splicing regulator 2; zinc finger protein |

tory levels were associated with OS [122]. Another study showed that miR-30e-5p was significantly downregulated in NSCLC tissues while miR-30e-3p was elevated in the serum of NSCLC patients as compared to healthy subjects. However, serum levels had no association with any clinical features or survival [118]. Further, miR-30b and miR-30c may act as a predictive biomarker for intrinsic erlotinib resistance; it might be useful in screening around 30% of non-responders to the drug despite *EGFR* mutation. Lower pre-treatment level of miR-30b was associated with enhanced PFS and OS after erlotinib treatment in NSCLC adenocarcinoma patients with activating *EGFR* mutation [125]. miR-30b/c also act as prognostic biomarkers for PFS and OS of first-line TKIs treatment [135]. A single study has checked the levels of miR-30a in circulation, and they found it to be elevated in NSCLC patients as compared to healthy subjects [118]. Besides, miR-30 has been checked along with other miRNAs for its potential as a part of a panel of sig-

nature miRNAs. A signature miRNA panel with upregulated miR-205-5p and miR-3917 and downregulated miR-27a-5p, miR-30a-3p, miR-30a-5p, miR-30c-2-3p, and miR-30d-5p indicates the enhanced risk of lung cancer [121]. Additionally, miR-30d was one of the four miRNAs along with miR-486, miR-1, and miR-499 associated with OS of NSCLC adenocarcinoma patients treated with surgery and adjuvant chemotherapies [136].

Further, Single nucleotide polymorphisms (SNPs) in miRNA seed region, genes, regulatory regions and its binding sites as observed in several studies are added determinants of its expression and activity [137]. Such SNPs can also increase the risk and aggressiveness of cancer by altering the function of miRNAs [138]. In a case-control study performed by Xie *et al.* [139], rs763354 in miR-30a was found to be significantly associated with NSCLC risk, but no association was observed in survival analysis. However, SNP in the flanking region of pre-miR-30c-1 (rs928508)

Table 5. Significant pathway terms miR-30 validated targets using KEGG pathway analysis by DAVID.

| Category | Term | Count | % | <i>p</i> value | Genes | List total | Pop hits | Pop total | Fold enrichment | Bonferroni | Benjamini | FDR |
|--------------|---|-------|-------|----------------|---------------------------------|------------|----------|-----------|-----------------|-------------|-------------|-------------|
| KEGG_PATHWAY | hsa04722: Neurotrophin signaling pathway | 4 | 12.5 | 0.002456001 | <i>BDNF, ABL1, PIK3CD, TP53</i> | 17 | 120 | 6879 | 13.48823529 | 0.218001303 | 0.136238747 | 0.13487636 |
| KEGG_PATHWAY | hsa05020: Prion diseases | 3 | 9.375 | 0.002724775 | <i>NOTCH1, HSPA5, NCAM1</i> | 17 | 34 | 6879 | 35.70415225 | 0.238792576 | 0.136238747 | 0.13487636 |
| KEGG_PATHWAY | hsa05202: Transcriptional misregulation in cancer | 4 | 12.5 | 0.006235795 | <i>SMAD1, ERG, TP53, RUNX2</i> | 17 | 167 | 6879 | 9.692145122 | 0.465023211 | 0.207859847 | 0.205781249 |
| KEGG_PATHWAY | hsa05220: Chronic myeloid leukemia | 3 | 9.375 | 0.011792009 | <i>ABL1, PIK3CD, TP53</i> | 17 | 72 | 6879 | 16.86029412 | 0.694623124 | 0.294800222 | 0.29185222 |
| KEGG_PATHWAY | hsa05206: MicroRNAs in cancer | 4 | 12.5 | 0.026640176 | <i>NOTCH1, ABL1, VIM, TP53</i> | 17 | 286 | 6879 | 5.659399424 | 0.932804271 | 0.454713559 | 0.450166423 |
| KEGG_PATHWAY | hsa04919: Thyroid hormone signaling pathway | 3 | 9.375 | 0.02853579 | <i>NOTCH1, PIK3CD, TP53</i> | 17 | 115 | 6879 | 10.55601023 | 0.94470568 | 0.454713559 | 0.450166423 |
| KEGG_PATHWAY | hsa05169: Epstein-Barr virus infection | 3 | 9.375 | 0.031829949 | <i>PIK3CD, VIM, TP53</i> | 17 | 122 | 6879 | 9.950337512 | 0.96063009 | 0.454713559 | 0.450166423 |

was found to a predictor in survival analysis and may act as a prognostic biomarker [140]. Although the above biomarker studies seem promising for translation to bedside, none has reached the stage of clinical trials indicating the need for advanced research in this area.

6. Future prospect

To further understand the significance of miR-30 family in NSCLC, we performed target search under the database miRTarBase 80, (2020) [141]. We selected only the experimentally validated targets of miR-30 family by luciferase reporter assay (Table 4). We found a total of 33 target genes validated till now in different pathophysiological conditions. Next, using the database for annotation, visualization, and integrated discovery (DAVID), we performed functional annotation clustering and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis [142]. Prominently enriched gene ontology cluster was related to transcription regulation and DNA binding with the enrichment score of 3.26, suggesting that miR-30 family may mostly regulate other transcription factors. The other highly enriched clusters broadly include zinc finger, splicing, transcriptional regulation apoptosis and proliferation (Supplementary Table 1). The KEGG pathway analysis revealed that Neurotrophin signaling pathway was the most significantly ranked according to *p* value (0.0025). Other significant terms included prion diseases, transcriptional misregulation in cancer, chronic myeloid leukemia, miRNAs in cancer, thyroid hormone signaling pathway and Epstein-Barr virus infection (Table 5). Neurotrophins are growth factors, best characterized for their involvement in neuronal survival, differentiation and conduction. They are associated with an array of neuronal diseases like Alzheimer's disease, Parkinson's disease and Brain tumour. Neurotrophin signalling has been recently recognized in lung health, but its role is weakly characterized [143]. The role of miR-30 in the regulation of neurotrophin signalling in NSCLC is also mostly unknown. Hence, examining these unexplored areas in NSCLC may shed more light in understanding the complex molecular aspects of the disease.

7. Conclusions

Accumulating studies have revealed that miR-30 family is abnormally expressed in several tumours, including lung cancer particularly, NSCLC. All sister miRNAs of miR-30 family have been studied to understand their role in NSCLC. Functionally, it can regulate cell proliferation, metastasis, EMT, cell cycle, and other prominent tumorigenic pathways. Even though its potential role has been observed in relation to smoking, the studies are minimal, and its exact function is unclear.

Moreover, its role has not been substantiated in chronic obstructive pulmonary disease (COPD), the most prominent associated illness along with lung cancer, suggesting that its absence may have a transforming potential and it might possess a disease-specific role in carcinogenesis. The review of the literature also indicates only limited *in vivo* studies in NSCLC. Studies reveal its enormous potential to be a diagnostic and prognostic biomarker, highlighting its clinical significance and translational value. Although advanced research is required to validate its role, the miR-30 family may be a ray of hope for better diagnosis and treatment of lung cancer.

8. Author contributions

SK participated in literature review, interpretation, drafting of the manuscript; NB and IK participated in reviewing of the manuscript; RCK participated in interpretation and critical review of the manuscript.

9. Ethics approval and consent to participate

Not applicable.

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12. Conflict of interest

The authors declare no conflict of interest.

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Send correspondence to: Chandrahas Koumar Ratnacaram, Yenepoya Research Centre, Yenepoya (Deemed to be University), University Road, Derlakatte, Mangalore, 575018 Karnataka, India, E-mail: rckoumar@yenepoya.edu.in