A Comprehensive Review on Function of miR-15b-5p in Malignant and Non-Malignant Disorders

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miR-15b-5p is encoded by MIR15B gene. This gene is located on cytogenetic band 3q25.33. This miRNA participates in the pathogenesis of several cancers as well as non-malignant conditions, such as abdominal aortic aneurysm, Alzheimer’s and Parkinson’s diseases, cerebral ischemia reperfusion injury, coronary artery disease, dexamethasone induced steatosis, diabetic complications and doxorubicin-induced cardiotoxicity. In malignant conditions, both oncogenic and tumor suppressor impacts have been described for miR-15b-5p. Dysregulation of miR-15b-5p in clinical samples has been associated with poor outcome in different kinds of cancers. In this review, we discuss the role of miR-15b-5p in malignant and non-malignant conditions.

Keywords: miR-15b-5p, cancer, biomarker, expression, malignance

INTRODUCTION

microRNAs (miRNAs) are a category of non-coding RNA with sizes about 20-24 nucleotide which participate in post-transcriptional control of gene expression (1). This effect is exerted through modulation of stability and translation of mRNAs. The primary transcripts produced by RNA polymerase II have 5’-cap and 3’-polyadenylated tail. Then, Drosha ribonuclease III enzyme cleaves this transcript to make the stem-loop precursor miRNA with an estimated size of 70 nucleotides (2). Finally, this transcript is processed by the Dicer ribonuclease to make the mature miRNA which can be combined into the RNA-induced silencing complex. Through incorporation into this complex, miRNAs can recognize their target transcript in a base pairing-dependent process resulting in suppression of translation or destabilization of transcript (3).

MIR15B gene is located on cytogenetic band 3q25.33 and encodes hsa-mir-15b. This miRNA participates in the pathogenesis of several cancers as well as non-malignant conditions, including cardiovascular disorders, neuropsychiatric diseases and metabolic conditions. This miRNA has been reported to exert oncogenic or tumor suppressor effects in different malignancies. We have searched the literature and discussed the role of miR-15b-5p in malignant and non-malignant conditions.
MIR-15B-5P IN CANCERS

Cell Line Studies

In bladder cancer cell lines, the long non-coding RNA (lncRNA) MAGI2-AS3 acts as a molecular sponge for miR-15b-5p. In fact, MAGI2-AS3 exerts its tumor suppressor role in bladder cancer through decreasing level of this miRNA. Meanwhile, miR-15b-5p has been found to target the tumor suppressor gene CCDC19. Taken together, MAGI2-AS3/miR-15b-5p/CCDC19 axis has been revealed to regulate progression of bladder cancer (4).

An *in vitro* experiment in breast cancer cells has shown that miR-15b-5p silencing could restrain cell proliferation and invasiveness and induce apoptosis, while its up-regulation has exerted the opposite impacts. Notably, heparanase-2 (HPSE2) has been acknowledged as the target of miR-15b-5p in breast cancer cells, through which this miRNA applies its effect (5).

In cervical cancer cells, level of the tumor suppressor lncRNA FENDRR has been shown to be decreased. This lncRNA has binding sites for miR-15a-5p and miR-15b-5p, two miRNAs that can down-regulate expression of Tubulin alpha1A (TUBA1A). Taken together, FENDRR/miR-15a/b-5p/TUBA1A molecular route has been proved to regulate progression of cervical cancer (6).

Expression of miR-15b-5p has been reported to be surged in colon cancer cells. Treatment of HT-29 cells with a PNA against miR-15b-5p has been shown to reduce cell proliferation and activate the pro-apoptotic pathway (7). Another research in colon cancer cells has displayed that SIRT1 suppresses metastatic ability of cells through decreasing expression of miR-15b-5p. In fact, SIRT1 disrupts the regulatory effect of AP-1 on activation of expression of miR-15b-5p *via* deacetylating this activation factor. miR-15b-5p can target the transcript of a central enzyme in the fatty acid oxidation, namely acyl-CoA oxidase 1 (ACOX1). Taken together, SIRT1/miR-15b-5p/ACOX1 axis has been identified as a functional route in regulation of metastatic ability of colorectal cancer cells (8).

*Figure 1* displays the oncogenic role of miR-15b-5p in bladder, breast, cervical, colorectal, liver, oral, ovarian, prostate and gastric cancers.

In contrast to the previously mentioned experiment in colorectal cancer cells (7), Zhao et al. have shown that miR-15b-5p has a tumor suppressor impact in this cancer. Notably, miR-15b-5p can enhance 5-fluorouracil (5-FU)-induced apoptosis in these cells and reversed the resistance of colorectal cancer cells to this therapeutic agent. Mechanistically, miR-15b-5p exerts this impact through modulating activity of the NF-κB signaling *via* decreasing NF-κB1 and IKK-α levels. miR-15b-5p has been found to target the anti-apoptosis transcript XIAP (9).

*In vitro* experiments in neuroblastoma cells have shown that up-regulation of miR-15a-5p, miR-15b-5p or miR-16-5p can reduce expression of MYCN transcript and N-Myc protein. On the other hand, suppression of these miRNAs could lead to enhancement of MYCN transcripts and N-Myc protein level, along with increasing half-life of its mRNA. The interaction between these miRNAs and MYCN mRNA has been proved through conducting immunoprecipitation and luciferase reporter assays. Notably, up-regulation of these miRNAs has diminished proliferation, migration, and invasiveness of neuroblastoma cells (17). *Figure 2* shows tumor suppressor
| Tumors                      | Interactions                                                                 | Cell line                                                                 | Function                                                                 | Reference |
|----------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------|
| Bladder cancer             | MAG22-AS3 and CCDC19                                                          | EJ, T24 and RT4, SV-HUC-1                                                 | ↑↑ MAG22-AS3 (which sponges mir-15b-5p): ↓ proliferation, ↓ migration and ↓ invasion | (4)       |
| Breast cancer              | HPSE2                                                                        | MDA-MB-231, MCF-7, 293T                                                  | Δ mir-15b-5p: ↓ proliferation, ↓ colony formation, ↓ migration and ↓ invasion, ↑ apoptosis | (5)       |
| Cervical cancer            | FENDRR, TUBA1A                                                               | HeLa, SiHa, CaSki, C33A, Ect1-E6E7                                       | ↑↑ FENDRR (which sponges mir-15b-5p): ↓ proliferation, ↓ migration and ↓ invasion, and ↓ cell viability, and ↑ apoptosis | (6)       |
| Colorectal cancer          | NF-κB1 and IκK-α                                                             | NCM460, SW620, HCT116, DLD1, SW116                                       | ↑↑ NF-κB1 and IκK-α: ↓ proliferation, ↓ migration, ↓ invasion, and ↓ cell viability, and ↑ apoptosis | (7)       |
| Cervical cancer            | FENDRR, TUBA1A                                                               | HeLa, SiHa, CaSki, C33A, Ect1-E6E7                                       | ↑↑ FENDRR (which sponges mir-15b-5p): ↓ proliferation, ↓ migration and ↓ invasion, and ↓ cell viability, and ↑ apoptosis | (6)       |
| Gastric cancer             | PAQR3                                                                        | AGS, BGC-823, SGC-7901, MGC-803                                          | ↑↑ PAQR3: ↓ proliferation and ↓ invasion                                  | (8)       |
| Glioblastoma multiforme    | U251                                                                          |                                                                           | Combo-therapy using PNA-a15b and SFN via interfering with mir-15b-5p could be used as a treatment for Glioblastoma multiforme to stimulate apoptosis. | (9)       |
| Hepatocellular carcinoma   | OIP5, AKT/tORC1 and β-catenin signaling pathways                             | HepG2, Hep3B, SK-HEP-1, Chang liver and THLE2, Huh7                     | Δ OIP5 [a target of mir-15b-5p]: ↓ migration, ↓ invasion and ↓ EMT process via mTORC1 and GSK-3β/β-catenin signaling | (10)      |
| Laryngeal cancer           | TXNIP                                                                        | HEP-2                                                                    | ↑↑ TXNIP: ↓ proliferation and ↓ invasion                                  | (11)      |
| Liver cancer               | Axin2                                                                         | HepG2 and Huh7, Hep3B and HCC-M3                                       | ↑↑ Axin2: ↓ proliferation and ↓ invasion                                   | (12)      |
| Neuroblastoma              | MYCN                                                                          | SK-N-BE (2), NB-19, SH-EP Tet21N, CHLA-136                               | ↑↑ MYCN: ↓ proliferation, ↓ migration, and ↓ invasion of NB cells         | (13)      |
| Non-small cell lung cancer | SNHG16, PRPS1                                                                |                                                                           | ↑↑ SNHG16: ↓ proliferation, ↓ migration, and ↓ invasion of NB cells       | (14)      |
| Oral squamous cell carcinoma| PTPN4, STAT3 pathway                                                         | SCC-4, UM-1, CAL-27, OSC-4                                               | ↑↑ PTPN4, STAT3 pathway: ↓ proliferation, ↓ migration, and ↓ invasion and ↓ apoptosis | (15)      |
| Oral tongue squamous cell carcinoma| TRIM14                                                                      | SCC25                                                                    | ↑↑ TRIM14: ↓ proliferation and ↓ invasion                                  | (16)      |
| Osteosarcoma               | PDK4                                                                          | hFOB1,19, MNNG-HOS, Saos-2, MGC83, U-2OS                                 | ↑↑ PDK4: ↓ proliferation and the Warburg effect by suppressing PDK4 expression | (17)      |
| Ovarian cancer             | TRPM2-AS and PPM1D                                                            | OS cells                                                                  | Δ TRPM2-AS (which sponges mir-15b-5p): ↓ viability, ↓ proliferation, ↓ migration and ↓ apoptosis | (18)      |
| Prostate cancer            | RECK                                                                         | A2780, OVCA429, IOSE80                                                  | ↑↑ RECK: ↓ proliferation and ↓ colony formation, ↓ apoptosis             | (19)      |
| Thyroid carcinoma          | G3D2, MMP2 and MMP9                                                           | FTC133, SW1736, K1, Nthy-ori3-1                                         | ↑↑ G3D2, MMP2 and MMP9: ↓ proliferation and ↓ invasion                    | (20)      |

↑ Up-regulation; ↓ Down-regulation.
role of miR-15b-5p in thyroid cancer, hepatocellular carcinoma, neuroblastoma, osteosarcoma and prostate cancer.

**Animal Studies**
Lovat et al. have produced miR-15b/16-2 knockout mice for the purpose of identification of the role of this cluster. This intervention has led to development of B-cell lymphomas by age 15–18 month possibly through modulation of expression of Cyclins D2 and D1, and IGF1R. These genes participate in the regulation of proliferation and antiapoptotic pathways. Taken together, this cluster has been shown to have a tumor suppressor role in mice models of B-cell lymphoma (28).

In xenograft models of bladder cancer, up-regulation of MAGI2-AS3 has reduced tumor volume possibly through decreasing expression of miR-15b-5p (4). Up-regulation of FENDRR, another miR-15b-5p-sponging lncRNA has exerted similar effects in xenograft models of cervical cancer (6). In colorectal cancer cells, a single study has shown that over-expression of miR-15b-5p improves sensitivity of cells to 5-FU (9). On the other hand, another study has indicated that SIRT1 decreases metastasis through suppression of miR-15b-5p transcription (8). Moreover, miR-15b-5p has been demonstrated to decrease expression of PD-L1, suppress tumorigenic potential of colorectal cancer cells and increase anti-PD-1 sensitivity in colitis-associated cancer and APCmin/+ models of colorectal cancer (10).

In an animal model of osteosarcoma, over-expression of miR-15b-5p has been associated with reduced cell proliferation (22).

**Human Studies**
Expression assays in clinical samples obtained from patients with bladder cancer, breast cancer, gastric cancer, oral squamous cell carcinoma and prostate cancer have shown up-regulation of miR-15b-5p. On the other hand, this miRNA has been found to be down-regulated in head and neck cancer squamous cell carcinomas, neublastoma and thyroid cancer samples. Different studies in colorectal cancer and hepatocellular carcinoma sample have shown contradictory expression patterns (Table 3). Moreover, dysregulation of expression of miR-15b-5p has been associated with poor clinical outcome in bladder cancer, breast cancer, head and neck/oral squamous cell carcinoma, hepatocellular carcinoma and neuroblastoma.

**ROLE OF MIR-15B-5P IN NON-MALIGNANT CONDITIONS**

**Cell Line Studies**
In vitro experiments in vascular smooth muscle cells (VSMCs) have shown that up-regulation of miR-15b-5p suppresses cell proliferation and induces apoptosis, while its knock down leads to opposite results. These effects are possibly mediated through suppression of ACSS2. Transfection of these cells with miR-15b-5p...
TABLE 2 | Summary of animal studies on the role of miR-15b-5p in cancers (Δ, knock-down or deletion).

| Tumors                      | Animals                                      | Results                                                                 | Reference |
|-----------------------------|----------------------------------------------|-------------------------------------------------------------------------|-----------|
| Bladder cancer              | 4-week-old female BALB/c nude mice           | ↑↑ MAI92-AS3: ↑ tumor volume and ↓ tumor weight                         | (4)       |
| Breast cancer               | 5-week-old female BALB/c nude mice           | Δ miR-15b-5p: ↓ tumorigenic ability                                       | (5)       |
| Cervical cancer             | 6-week-old male BALB/c nude mice             | ↑↑ FENDRR (which sponges mir-15b-5p): ↓ tumor volume and ↓ tumor weight | (6)       |
| Colorectal cancer           | Four-week-old female athymic nude mice       | ↑↑ miR-15b-5p: ↓ sensitivity of colon cancer cells to 5-FU and ↓ apoptosis via the NF-κB pathway | (9)       |
|                             | 4-6 weeks old BALB/c nude mice               | ↑↑ SIRT1: ↓ metastasis by suppressing mir-15b-5p transcription via AP-1 | (8)       |
| Hepatocellular carcinoma    | Four-week-old female BALB/c nude mice        | Δ miR-15b-5p: ↑ tumorigenesis and ↓ PD-L1 levels                          | (10)      |
| Neuroblastoma               | Six-week-old NOD mice                        | ↑↑ miR-15b-5p: ↓ tumor size and ↓ tumor weight                          | (17)      |
| Non-small cell lung cancer  | Balb/c nude mice                             | Δ CERS6-AS1 (which sponges miR-15b-5p): ↓ tumor growth                  | (11)      |
| Oral squamous cell carcinoma| 5-week-old female specific-pathogen-free mice| Δ OIP5 (a target of mir-15b-5p): ↓ tumor growth and ↓ metastasis        | (12)      |
| Osteosarcoma                | 5-week-old male BALB/c nude mice             | ↑↑ miR-15b-5p: ↓ tumor growth, ↓ tumor volume and ↓ tumor weight       | (15)      |
| Prostate cancer             | PC3 xenograft tumor model                     | ↓↓ miR-15b-5p: ↓ proliferation                                          | (22)      |
|                            |                                              | Δ miR-15b-5p: ↓ tumor volume and ↓ tumor weight                         | (25)      |

↑ Up-regulation; ↓ Down-regulation.

miR-15b-5p has also been shown to mediate the anti-amyloid effect of curcumin in an in vitro model of Alzheimer’s disease through influencing expression of the amyloid precursor protein (36). Moreover, the antiangiogenic effect of isopimpinellin has been attributed to its impact on induction of miR-15b-5p expression and subsequent down-regulation of angiogenic stimulators (37).

In addition, miR-15b-5p has been shown to mediate the effects of LINCO00473 in cerebral I/R injury. Experiments in a cellular model of cerebral I/R injury has shown down-regulation of LINCO00473 in these cells. Up-regulation of this lncRNA has reversed the effects of oxygen glucose deprivation/reperfusion on cell viability and apoptosis as well as ROS levels. Mechanistically, LINCO00473 acts as a molecular sponge for miR-15b-5p and miR-15a-5p and regulates expression of SRPK1 (38). Table 4 shows summary of cell line studies on the role of miR-15b-5p in non-malignant conditions.

Animal Studies
Animal studies have highlighted the role of miR-15b-5p in different cellular processes and disorders such as angiogenesis, coronary artery disease, diabetic nephropathy, diabetic retinopathy, myocardial I/R injury, necroptosis and inflammation, Parkinson’s disease and trachea inflammatory injury (Table 5). For instance, overexpression of miR-15b-5p has considerably suppressed arteriogenesis and angiogenesis in animal models through targeting AKT3. Remarkably, siRNA-mediated silencing of AKT3 has inhibited arteriogenesis and the rescue of blood perfusion following femoral ligation in animals (42). Another animal study has shown that silencing of the miR-15b-5p-sponging lncRNA MALAT1 decreases atherosclerotic process (43). miR-15b-5p has also been shown to affect diabetic nephropathy and retinopathy in animals. Assessment of transcriptome of high glucose-exposed mouse mesangial cells has shown the effect of miR-15b-5p and its downstream target BCL-2 in regulation of high glucose-induced apoptosis. Besides, db/db mice has been shown to have higher levels of urinary miR-15b-5p (47).

Human Studies
Different experiments in human samples obtained from patients with acute mountain sickness, asthma-COPD overlap, coronary artery disease, diabetic foot ulcers, diabetic nephropathy, late pulmonary complications, obstructive sleep apnea and Parkinson’s disease have shown dysregulation of miR-15b-5p levels (Table 6).

This miRNA might participate in the pathoetiology of acute mountain sickness. Levels of miR-15b-5p in the saliva have been found to be higher in individuals being resistant to this condition compared to susceptible ones. Combination of levels of miR-134-3p and miR-15b-5p could discriminate between these two groups. Thus, salivary levels of miR-134-3p and miR-15b-5p have been suggested as non-invasive markers for prediction of acute mountain sickness prior to exposure to high altitude (71).

Although in vitro studies indicated possible role of miR-15b-5p in the pathogenesis of Alzheimer’s disease (36), serum levels of miR-15b-5p were not significantly different between patients with Alzheimer’s disease and healthy subjects (72).

miR-15b-5p has been among miRNA having lower expression in asthma-COPD overlap patients. This miRNA can distinguish between asthma-COPD overlap patients and individuals with either asthma or COPD. In fact, miR-15b-5p has been shown to be superior to other miRNAs in separation of patients with asthma-COPD overlap from similar conditions (73).
| Tumors | Specimens | Expression (Tumor vs. Normal) | Kaplan-Meier analysis (as a result of dysregulation in mir-15b-5p) | Multivariate/Univariate Cox regression | Clinicopathologic characteristics | Method by which RNA was detected | Reference |
|--------|-----------|-------------------------------|---------------------------------------------------------------|-------------------------------------|-----------------------------------|----------------------------------|-----------|
| Bladder cancer | 10 patients with and without BC included 3 healthy persons and 7 patients with other urologic diseases TCGA database 58 pairs of tumor tissues and ANCTs | upregulated | – | – | – | ExiLENT SYBR® Green master mix (29) |
| Breast cancer | 6 pairs of tumor tissues and ANCTs TCGA databases | upregulated | Poorer OS | – | – | PrimeScript RT-PCR kit (4) |
| Cervical cancer | 53 pairs of tumor tissues and ANCTs | Downregulation of FENDRR (which sponges mir-15b-5p) | – | – | – | SYBR Green kit (6) |
| Colorectal cancer | 23 pairs of tumor tissues and ANCTs TCGA database | downregulated | – | – | – | TransStart SYBR Green supermix (9) |
| Colorectal cancer | 94 tumor tissues | downregulation in SIRT1 which suppresses mir-15b-5p transcription via AP-1 | – | – | – | – (8) |
| | 110 pairs of tumor tissues and ANCTs TCGA database: MSS CRC samples GEPIA database | upregulation of CERS6-AS1 (which sponges mir-15b-5p) | – | – | – | – (11) |
| Gastric cancer | 40 pairs of tumor tissues and ANCTs 100 patients and 100 healthy controls | upregulated | – | – | degree of tumor invasion and lymph node metastasis and distant metastasis | PrimeScript™ RT reagent kit (12) |
| Head and neck cancer squamous cell carcinomas | 43 HNSCC patient in explorative phase 51 HNSCC patient in validation phase | downregulated | Shorter locoregional RFS miR-15b-5p was found to be an independent predictive factor of LRC in HNSCC patients. | – | – | TaqMan stem-loop (30) |
| Hepatocellular carcinoma | TCGA and GEO databases 991 HCC and 456 adjacent non-HCC tissue samples GEO database (GSE36411: 42 pairs of tumor tissues and ANCTs) 46 pairs of tumor tissues and ANCTs Phase I: 6 pairs of tumor tissues and ANCTs (from 6 HCC patients) Phase II: 10 patients Phase III: 37 HCC patients, 29 cirrhosis patients, and 31 healthy controls 28 pairs of tumor tissues and ANCTs | upregulated | – | – | – | – (31) |
| | GEO database (GSE76903: 20 pairs of tumor tissues and ANCTs) | Upregulation of OIP5 (a target of miR-15b-5p) | – | – | – | – (12) |
| | 46 pairs of tumor tissues and ANCTs | downregulated | – | – | – | SYBR Green (14) |
| | Phase I: 6 pairs of tumor tissues and ANCTs (from 6 HCC patients) Phase II: 10 patients Phase III: 37 HCC patients, 29 cirrhosis patients, and 31 healthy controls 28 pairs of tumor tissues and ANCTs | Overexpression in tumor tissues and preoperative plasmas, and downregulation in postoperative plasma | – | – | – | All-in-One™ miRNA qRT-PCR Detection Kit (32) |
| | 28 pairs of tumor tissues and ANCTs | upregulated | – | – | – | SYBR Premix Ex Taq II on an FTC-3000TM System (15) |
| | GSE27462 (5 pairs of tumor tissues and ANCTs) | | – | – | – | – (33) |

(Continued)
| Tumors                          | Specimens                                                                 | Expression (Tumor vs. Normal) | Kaplan-Meier analysis (as a result of dysregulation in mir-15b-5p) | Multivariate/Univariate cox regression | Clinicopathologic characteristics | Method by which RNA was detected | Reference |
|--------------------------------|---------------------------------------------------------------------------|------------------------------|---------------------------------------------------------------------|---------------------------------------|-------------------------------------|----------------------------------|-----------|
| Liver cancer                   | 69 pairs of tumor tissues and ANCTs                                       | upregulated                  | Poorer OS                                                          | TNM stage and tumor capsular infiltration |                                     | SYBR Premix Ex Taq                | (14)      |
| Neuroblastoma                  | Two cohort: 88 NB patients and 105 NB patients                           | downregulated                | Poorer OS                                                          |                                       |                                     | SYBR green mix (Bio-Rad) for mRNA expression or TaqMan Universal Fast PCR master mix | (17)      |
|                                | 46 neuroblastoma samples and 28 normal tissues                           | downregulated                | _                                                                  | _                                     |                                     | _                                | (18)      |
| Non-small cell lung cancer     | 37 pairs of tumor tissues and ANCTs                                       | downregulated                | _                                                                  | _                                     |                                     | _                                | (19)      |
| Oral squamous cell carcinoma   | TCGA database                                                             | upregulated                  | Poorer OS                                                          | tumor stage, TNM stage, and tumor metastasis | SYBR Premix Ex Taq II               | (20)    |
| Ovarian cancer                 | TCGA and genotype-tissue expression (GTEx) databases                     | downregulation in TTN-AS1    | _                                                                  | _                                     |                                     | _                                | (24)      |
| Prostate cancer                | TCGA database: 495 patients and 52 pairs of tumor tissues and ANCTs       | upregulated                  | _                                                                  | _                                     |                                     | _                                | (25)      |
| Squamous cell carcinoma        | 10 patients and 30 healthy controls                                      | downregulated                | _                                                                  | _                                     |                                     | _                                | (34)      |
| Thyroid carcinoma              | Cancer Genome Atlas project database: 509 patients and 58 healthy controls| downregulated                | Poorer OS                                                          | _                                     |                                     | _                                | (27)      |
### TABLE 4 | Summary of cell line studies on the role of miR-15b-5p in non-malignant conditions (Δ, knock-down or deletion; DOX, doxorubicin; HG, High glucose; SHF, secondary hair follicle; ER, endoplasmic reticulum; EVs, extracellular vesicles).

| Disease type | Interactions | Cell line | Function | Reference |
|-------------|--------------|-----------|----------|-----------|
| Abdominal aortic aneurysm | ACSS2 and PTGS2 | Human aortic VSMCs (T/G HA-VSMC cell line) | ↑↑ miR-15b-5p: ↑ proliferation and ↓ apoptosis of aortic VSMCs via targeting the ACSS2/PTGS2 axis | (35) |
| Alzheimer’s disease | amyloid precursor protein and amyloid-β | Human umbilical Vein Endothelial Cell (HUVEC) | Curcumin treatment: ↑ mir-15b-5p and ↓ amyloid precursor protein and ↓ amyloid-β | (36) |
| Angiogenesis | ... | Human umbilical Vein Endothelial Cell (HUVEC) | Isoprinpatrin: ↓ proliferation, ↓ invasion, ↓ migration, and tube formation via increasing mir-15b-5p levels and decreasing angiogenic stimulators | (37) |
| Asthma | YAP1 | ASM cells | ↑↑ miR-15b-5p: ↑ proliferation, migration, inflammation response, and ECM deposition of TNF-α-induced ASM cells | (39) |
| Atherosclerosis | circCHFR and GADD45G | HUVECs | Uregulation of miR-15b-5p was found to reduce apoptosis, proinflammatory cytokine secretion, and improved cell survival via targeting GADD45G. | (40) |
| Cerebral I/R injury | LINCO0473, SRPK1 | Neuro-2a (N2a) cells | ↑↑ miR-15b-5p: ↑ cell viability, ↓ apoptosis and ↓ ROS level induced by OGD/R | (38) |
| Clopidogrel-induced liver injury | AKT3 | Human umbilical vein endothelial cells (HUVECs) | ↑↑ miR-15b-5p: ↑ migration and ↓ proliferation of endothelial cells | (42) |
| Coronary artery disease | MALAT1 and MAPK1, mTOR signaling pathway | HEK 293T cells | Δ MALAT1 (which sponges mir-15b-5p): ↑ cell viability, ↓ autophagy and ↓ development of CAD | (43) |
| Diabetic foot ulcers | ENST00000608794, PDK4 | dexamethasone treated HepG2 cell lines | Δ ENST00000608794 (which sponges mir-15b-5p): ↓ dexamethasone induced steatosis | (44) |
| Diabetic foot ulcers | IKBKB and WEE1 | human keratinocytes | ↑↑ miR-15b-5p: ↓ dexamethasone induced steatosis | (45) |
| Diabetic nephropathy | JNK and Akt/mTOR pathway | HK-2 and HK-5 cells | High glucose treatment: ↑ expression of mir-15b-5p in HK-2 cells | (46) |
| Diabetic nephropathy | BCL-2 | Mouse MCs (CRL1927) and human embryonic kidney (HEK) 293 cells | High glucose treatment: ↑↑ mir-15b-5p expression in mouse MCs, so ↑ mouse MC apoptosis by targeting BCL-2 | (47) |
| Diabetic retinopathy | CDKN2B-AS1 and WNT2B | HMCs | Δ miR-15b-5p: ↑ viability, ↑ cell cycle progression, ↑ ECM accumulation, ↑ inflammatory response | (48) |
| Diabetic retinopathy | circ_001209, COL12A1 | human retinal vascular endothelial cells (HRVECs) | ↑↑ miR-15b-5p: ↑ viability, ↑ cell cycle progression, ↑ ECM accumulation, ↑ inflammatory response | (49) |
| Diabetic retinopathy | circ_001209, COL12A1 | human retinal vascular endothelial cells (HRVECs) | ↑↑ miR-15b-5p: ↑ viability, ↑ cell cycle progression, ↑ ECM accumulation, ↑ inflammatory response | (50) |
| Diabetic retinopathy | TNFα, SOCS3 and IGFBP-3 I | Human REC | ↑↑ miR-15b-5p: ↓ invasion, ↓ migration and ↓ tubular formation induced by HG | (51) |
| DOX-induced cardiotoxicity | Bmpr1a | H9c2 cardiomyocytes | High glucose induced apoptosis, ↑ oxidative stress and ↑ mitochondria damage | (52) |
| DOX-induced cardiotoxicity | Rab1A | HT22 cells | Steviane exposure: ↓ cell viability, and apoptosis and ↑ ER stress via increasing mir-15b-5p levels, thus inhibiting Rab1A | (53) |
| Endoplasmic reticulum stress mediated neurons apoptosis | HCAR, VEGF and MMP13 | BMSCs | HCAR sponges mir-15b-5p to regulate VEGF and MMP13, so induces endochondral bone repair in hypotrophic chondrocyte. | (54) |
| Fracture | Seman3A | mouse podocytes | ↑↑ miR-15b-5p: ↓ apoptosis, ↓ oxidative stress, and ↓ inflammatory response | (55) |
| High glucose-induced podocyte injury | IncRNA-599547, Wnt110b | dermal papilla cells (DPCs) of passage 3 of cashmere goat SHF | InCNA-599547 (which sponges mir-15b-5p) showed strongly high levels in dermal papilla of cashmere goat SHF. High levels of ↑↑ IncRNA-599547 (which sponges mir-15b-5p) was found to protect cardiomyocytes against ischemia-related apoptotic death. | (56) |
| Myocardial infarction | circ-Ttc3, Arf2 | human retinal vascular endothelial cells (HRVECs) | ↑↑ miR-15b-5p: ↑ viability, ↑ cell cycle progression, ↑ ECM accumulation, ↑ inflammatory response | (57) |

(Continued)
### TABLE 4 | Continued

| Disease type                          | Interactions                                      | Cell line             | Function                                                                                       | Reference |
|--------------------------------------|---------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------|-----------|
| Necroptosis and inflammation         | TGFβR3, TGF-β pathway                             | HD11 and DT40         | H2S exposure; † oxidative stress and activates the TGF-β pathway by regulating miR-15b-5p/TGFβR3 axis miR-15b-5p is upregulated in H2S-induced necroptosis and inflammation. | (58)      |
| Obstructive sleep apnea              | PTGS1-NF-κB-Sp1 signaling                        | human THP-1, HUVEC, and SH-SYSY cell lines | Δ miR-15b-5p: † IHR-induced oxidative stress and † MACA hyperactivity via targeting PTGS1-NF-κB-Sp1 signaling in OSA patients | (59)      |
| Osteoarthritis                       | LINC00662, GPR120                                 | rat chondrocytes      | LINC00662 is downregulated in osteoarthritis, so mir-15b-5p is upregulated and GPR120 is suppressed, thus inflammatory responses and apoptosis are induced. | (60)      |
| Parkinson’s disease                  | LINC00943 and RAB3IP SNHG1 and GSK3β Akt3         | SK-N-SH cells         | Δ LINC00943 (which sponges mir-15b-5p): † MPP+-caused decrease of cell viability so reduced MPP+-induced neuronal damage †† SNHG1 (which sponges mir-15b-5p): † MPP+ -induced cellular toxicity, † cell viability via mir-15b-5p/GSK3β axis | (61)      |
| Severe acute respiratory syndrome    | SNHG1, SIAH1 viral RdRp                           | SH-SYSY               | †† mir-15b-5p: † α-synuclein aggregation and † apoptosis via targeting SIAH1 † mir-15b-5p: † viral infection and † proliferation by targeting the RNA template component of SARS-CoV-2 RdRp | (62)      |
| Arthritis                            | IncrRS1 and IRS1                                 | DF-1 cells            | LncIRS1 (which sponges mir-15b-5p) was found to regulate myoblast proliferation and differentiation in vitro via increasing IRS1. | (63)      |
| Tendon injury                         | circRNA-Ep400, FGF-1/2 7/9                        | 293 T cells, fibroblasts and tenocytes | †† M2 macrophage-derived circRNA-Ep400 (which sponges mir-15b-5p): † fibrosis, † proliferation, and † migration | (64)      |

† Up-regulation; † Down-regulation.

### TABLE 5 | Summary of studies on the role of mir-15b-5p in non-malignant conditions (Δ, knock-down or deletion; MDA, malondialdehyde; ECs, endothelial cells; ACR, Albumin-to-Creatinine Ratio; H2S, Hydrogen sulfide).

| Disease Type                          | Animal models                                      | Results                                                                                       | Reference |
|--------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------|
| Angiogenesis                         | zebrafish embryos                                 | Isopimpinellin: † intersegmental vessels                                                                 | (37)      |
| Coronary artery disease              | 8-10-week-old male C57BL/6 mice                   | miR-15b-5p expression was decreased, because of a reduced expression in EC layer of collaterals and miR-15b-5p was mainly derived from ECs. | (42)      |
| Coronary atherosclerotic heart disease| Six-week old male ApoE−/− mice                    | Δ MALAT1 (which sponges mir-15b-5p): † atherosclerosis                                                                 | (43)      |
| Diabetic nephropathy                 | 5 db/m mice and 5 db/db mice                      | Higher urine miR-15b-5p levels were found in db/db mice. Urinary EV miR-15b-5p levels were positively associated with urinary ACR. With increased levels of circ_001209 (which sponges miR-15b-5p) retinal thickness was thinner in diabetic rats, and apoptosis was enhanced. | (44)      |
| Diabetic retinopathy                 | 80 Sprague–Dawley male rats                       | Δ mir-15b-5p: † arthritism, infract extent and apoptosis, † MDA content in the myocardial tissue by increasing levels of KCNJ2 (a target of mir-15b-5p) H2S exposure: † necroptosis and inflammation | (45)      |
| Myocardial ischemia                  | 6-8-week-old male C57/B6 mice                    | H2S exposure: † necroptosis and inflammation                                                                 | (46)      |
| Myocardial ischemia                  | 40 one-day-old Ross 308 male broilers             | mir-15b-5p: † MAPK-induced apoptosis by regulating Akt3 LncIRS1 (which sponges mir-15b-5p) was found to regulate muscle mass and muscle fibre cross-sectional area. | (47)      |
| Parkinson’s disease                  | five-week-old male C57BL/6 mice                   | Δ mir-15b-5p: † MPTP-induced apoptosis by regulating Akt3 LncIRS1 (which sponges mir-15b-5p) was found to regulate muscle mass and muscle fibre cross-sectional area. | (48)      |
| Skeletal muscle atrophy              | 1-day-old chicks                                  | H2S exposure: † mir-15b-5p miR-15b-5p reduced ATF2 levels to mediate METs release, which induces trachea inflammatory damage | (49)      |
| Trachea inflammatory injury          | Eighty one-day-old Ross 308 broilers divided into two groups (control group and H2S group) |                                                                         | (50)      |

† Up-regulation; † Down-regulation.
### TABLE 6 | Summary of human studies on the role of miR-15b-5p in non-malignant conditions (CAD, coronary atherosclerotic heart disease; CCC, coronary collateral circulation; ACR, albumin-to-creatine ratio; eGFR, Estimated Glomerular Filtration Rate; AMS, Acute mountain sickness; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; DN, diabetic nephropathy; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; DFU, Diabetic foot ulcers; FS, foot skin).

| Disease type | Numbers of clinical samples | Expression (Tumor vs. Normal) | Clinicopathologic characteristics of patients | Method by which RNA was detected | Reference |
|--------------|----------------------------|------------------------------|-----------------------------------------------|----------------------------------|-----------|
| Acute mountain sickness | 124 healthy men (75 AMS+ group and 49 AMS– group) | upregulated in AMS- group | _ | iQ™5 Real-Time PCR Detection System | (71) |
| Alzheimer’s disease | 50 AD patients and 50 healthy controls | no significant differences | _ | _ | (72) |
| Asthma-COPD overlap | Cohort 1: 6 patients with ACO and 6 patients with asthma; Cohort 2: 30 patients with asthma, 30 patients with COPD, or 30 patients with ACO | downregulated in ACO patients | _ | miScript SYBR Green PCR Ki | (73) |
| Atherosclerosis | 30 patients with atherosclerosis and 30 healthy controls | downregulated | _ | SYBR Green PCR kit | (40) |
| Coronary artery disease | 5 patients with poor CCC and 5 patients with good CCC; 20 patients with poor CCC and 18 patients with good CCC and 18 healthy controls | upregulated in patients with poor CCC | mR-15b-5p was associated with insufficient coronary collateral artery function. | SYBR Premix Ex Taq qRT-PCR assays | (42) |
| Coronary atherosclerotic heart disease | GEO database (GSE18608): 10 CAD patients and 4 healthy controls | downregulated | _ | SYBR green | (43) |
| Diabetic foot ulcers | 12 DFU and 12 FS specimens; 6 DFU and 6 FS specimens (GEO database GSE80178) | upregulated in DFU | _ | PerfeCTa® SYBR® Green SuperMix | (45) |
| Diabetic nephropathy | 85 type 2 diabetic patients and 39 healthy controls | upregulated | Urinary EV miR-15b-5p levels were found to be positively associated with urinary ACR, negatively associated with eGFR, and correlated with rapid decline in kidney function in humans. | _ | (47) |
| Late pulmonary complications | 34 DN patients and 34 healthy controls; 20 Sulfur mustard-exposed individuals and 20 healthy controls | downregulated | _ | SYBR Green | (48) |
| Obstructive sleep apnea | Discovery cohort: 16 OSA Patients and 8 healthy controls; Validation cohort: 20 Primary Snoring, 45 Treatment-Naïve OSA Patients, and 13 OSA Patients on CPAP | downregulated in OSA patients | mR-15b-5p was negatively associated with an apnea hypopnea index | NGS (Illumina MiSeq platform) and SYBR Green PCR kit | (59) |
| Parkinson’s disease | 10 patients and 5 healthy controls | upregulated | _ | ABI PRISM® 7500 Sequence Detection System | (63) |
In some conditions, dysregulation of this miRNA has been associated with clinicopathological parameters. For instance, in patients with coronary artery disease, dysregulation of miR-15b-5p has been associated with insufficient coronary collateral artery function (42). Moreover, in diabetic nephropathy, Urinary exosomal levels of miR-15b-5p have been positively associated with urinary albumin-to-creatinine ratio, negatively associated with eGFR, and correlated with speedy failure in kidney function (47).

DISCUSSION

miR-15b-5p is an example of miRNAs with dual roles in the carcinogenesis. While it is a putative oncogenic miRNA in bladder cancer, cancer, gastric cancer, oral squamous cell carcinoma and prostate cancer, it has been found to be down-regulated in head and neck cancer squamous cell carcinomas, neublastoma and thyroid cancer samples as compared with corresponding non-cancerous samples (75). Moreover, in colorectal cancer and hepatocellular carcinoma, different studies have reported contradictory results.

This miRNA also participates in the pathogenesis of several non-malignant conditions, such as abdominal aortic aneurysm, Alzheimer’s disease, Parkinson’s disease, cerebral I/R injury, coronary artery disease, dexamethasone induced steatosis, diabetic complications and doxorubicin-induced cardiotoxicity.

miR-15b-5p has been shown to be sponged by several lncRNAs, namely MAGI2-AS3, H19, SNHG1, SNHG16, TTN-AS1, PVT1, FENDRR, SSTR5-AS1, MALAT1, ENST00000608794, CDKN2B-AS1, LINC00473, LINC00662, LINC00943, LncRNA-599547 and CDKN2B-AS1 as well as the circular RNA Circ_001209. Thus, lncRNAs and circRNAs can affect expression of this miRNA. Other possible regulatory mechanisms for modulation of expression levels of miR-15b-5p should be clarified in future studies.

NF-κB, STAT3, AKT/mTORC1, CDC42/PAK1 and β-catenin signaling pathways are signaling pathways that mediate the effects of miR-15b-5p in the carcinogenesis. Notably, this miRNA could regulate response of cancer cells to 5-FU and anti-PD-1 drugs. Thus, therapeutics modalities affecting expression of miR-15b-5p can be considered as possible ways to combat resistance to anti-cancer agents. Evidence from in vitro and in vivo studies indicates that therapeutic intervention with miR-15-5p can be considered as possible ways to combat resistance to anti-cancer agents. Evidence from in vitro and in vivo studies indicates that therapeutic intervention with miR-15-5p can be considered as possible ways to combat resistance to anti-cancer agents. Evidence from in vitro and in vivo studies indicates that therapeutic intervention with miR-15-5p can be considered as possible ways to combat resistance to anti-cancer agents.

While the prognostic impact of dysregulation of miR-15b-5p has been confirmed in different types of cancer, there is no explicit evidence for application of this miRNA as a diagnostic marker in cancers. Since miRNAs dysregulation in the circulation provides a potential way for early non-invasive diagnosis of cancer, future studies should focus on evaluation of expression levels of miR-15b-5p in different biofluids during the course of cancer to provide insights into diagnostic role of this miRNA in cancer.

CONCLUSION

While the prognostic impact of dysregulation of miR-15b-5p has been confirmed in different types of cancer, there is no explicit evidence for application of this miRNA as a diagnostic marker in cancers. Since miRNAs dysregulation in the circulation provides a potential way for early non-invasive diagnosis of cancer, future studies should focus on evaluation of expression levels of miR-15b-5p in different biofluids during the course of cancer to provide insights into diagnostic role of this miRNA in cancer.

AUTHOR CONTRIBUTIONS

SG-F wrote the manuscript and revised it. MT supervised and designed the study. TK, HJ, MH and BH collected the data and designed the figures and tables. All authors read and approved the submitted version.

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