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MicroRNA-1: Diverse role of a small player in multiple cancers

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Abstract

The process of cancer initiation and development is a dynamic and complex mechanism involving multiple genetic and non-genetic variations. With the development of high throughput techniques like next-generation sequencing, the field of cancer biology extended beyond the protein-coding genes. It brought the functional role of noncoding RNAs into cancer-associated pathways. MicroRNAs (miRNAs) are one such class of noncoding RNAs regulating different cancer development aspects, including progression and metastasis. MicroRNA-1 (miR-1) is a highly conserved miRNA with a functional role in developing skeletal muscle precursor cells and cardiomyocytes, and acts as a consistent tumor suppressor gene. In humans, two discrete genes, *MIR1–1* located on 20q13.333 and *MIR1–2* located on 18q11.2 loci, encode for a single mature miR-1. Dysregulation or downregulation of miR-1 has been demonstrated in multiple cancers, including lung, breast, liver, prostate, colorectal, pancreatic, medulloblastoma, and gastric cancer. A vast number of studies have shown that miR-1 affects the multiple hallmarks of

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Author contributions

PK, NSE, and MWN were involved in the conception and design of the review. PK and NSE researched the data for the article and wrote the original draft of the manuscript. PK and NSE contributed equally to this manuscript. PK, NE, JAS, SKM, IL, RS, SKB, and MWN critically revised the manuscript. All authors read and approved the content of the manuscript before final submission.

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cancer like proliferation, invasion and metastasis, apoptosis, angiogenesis, chemosensitization, and immune modulation. The potential therapeutic applications of miR-1 in multiple cancer pathways provide a novel platform for developing anticancer therapies. This review focuses on the different antitumorigenic and therapeutic aspects of miR-1 including how it regulates tumor development and associated immunogenic functions.

Keywords

miR-1; immunoregulation; cancer therapeutics; chemosensitivity; miRNAs

1. Introduction

MicroRNAs (miRNAs or miRs) are short non-coding RNAs consisting 21–22 nucleotides that regulate various molecular pathways and triggering the endogenous RNA-interference (RNAi) by modulating the stability or inducing mRNA degradation [1–5]. The biogenesis of miRNAs follows a systematic process; RNA-polymerase II transcribed the initial stem-loop structure or primary miRNA strand in the nucleus [6, 7]. The miRNA hairpin structure, embedded within the stem-loop primary miRNA strand, is successively processed by DROSHA and DICER (both belong to the RNase III family), liberating the mature miRNA consisting of 21–22 nucleotides [6, 7].

The mature miRNA sequence is loaded to the RNA-induced silencing complex (RISC complex) and modulates gene expression or induces degradation by binding with the 3'-untranslated region (UTR) of the target gene. The primary mode of action for miRNA usually follows a slicer-independent mechanism in which they bind with 3'-UTR of mRNA with complete or incomplete complementarity and perform gene silencing [8–11]. Because miRNAs can act through low complementarity; thus, they could have multiple targets, but the primary safety check is the restriction of imperfect base pairing. Recent studies demonstrated that miRNAs also regulate the methylation of CpG islands (present in the promoter region of different genes) and thus, regulates the epigenetic transcriptional regulations [8–11]. Most of the miRs are highly conserved among species, suggesting the importance of this highly selective pressure for their crucial roles in development, evolution, and diseased conditions [12]. Their importance was further defined through peculiar observation that mice lacking DICER (the essential enzyme for mature miRNA production) showed embryonic lethality [13]. The miRs play diverse functions in physiological and pathophysiological progressions, including metabolism [14], neurological disorders [15], diabetes [16], infectious diseases [17, 18], muscular dystrophy [19], cell-cycle progression [20], cancer development and progression [21–24], and immunity [25–27]. Interestingly, miRs represent one of the largest collections of gene regulatory molecules; therefore, they constitute an important research axis to understand different mechanisms and for the development of different therapeutic strategies.

Based on aberrant expression, miRs can categorize into two major classes: upregulated and downregulated miRs. Studies demonstrated low and high expression of miRs in normal development and various disease conditions, including viral infections, immunological

disorders, and multiple types of cancers [12, 28–32]. In the case of cancer, a number of miRNAs fine-tuned the expression of oncogenes and tumor suppressors in response to a variety of extracellular signals [33–36]. The overexpression of various miRNAs has been reported in different cancers; however, the majority of miRs are found to be downregulated in multiple tumors, thus pointing towards the tumor-suppressing properties of miRs over oncogenic [4, 37, 38].

Among more than 2600 known human miRNAs (http://mirbase.org/), microRNA-1 (miR-1) is one of the highly conserved and most consistent tumor-suppressor or downregulated miRNA in various cancers [39]. In humans, two discrete genes, *MIR1–1* and *MIR1–2,* located on genomic locus 20q13.33 and 18q11.2, respectively, encode for a single mature miR-1 having 21 nucleotides (Figure 1 &2) [40, 41]. The initial studies of miR-1 showed that miR-1–1 and miR-1–2 were expressed in cardiomyocytes and precursor cells of skeletal muscles [40]. It controls the expression of various genes including, Kruppel-like factor 4 (KLF4), heat shock protein 60 (HSP60), heart and neural crest derivatives expressed 2 (HAND2, a transcription factor that regulates the development of cardiomyocytes), stanniocalcin 2 (STC2), and transforming growth factor-beta (TGF-β) signaling [40–45]. At the same time, miR-1 genes act as a direct target of muscle differentiation regulators, including serum response factor, myoblast determination protein 1 (MyoD), and myocyte enhancer factor-2 (Mef2) [40, 46]. MiR-1 is also reported to target histone deacetylase 4 (HDAC4), which acts as a transcriptional repressor of muscle-specific gene expression and promotes myogenesis [46]. The collective outcomes of different studies suggested that miR-1 plays an important role in cardiogenesis, cell cycle regulation, cardiac conduction, myogenesis, myoblasts differentiation, myocardial infarction, chronic obstructive pulmonary disease, and heart failure [47–54]. Apart from the critical role of miR-1 in the physiological functioning of the heart, smooth, and skeletal muscles, miR-1 dysregulation has been associated with multiple cancers and immune responses [41, 55, 56]. Since the different aspects or role of miRNAs has been reported and discussed extensively [36, 51, 55, 57–62], here in the present review, we particularly discuss and summarize the tumor-associated and immunogenic roles of miR-1 in multiple cancers.

2. Expression and role of miR-1 in different cancers

Several studies showed the downregulation or decreased expression of miR-1 in various human cancers, including liver cancer, lung cancer (LC), breast cancer (BC), colon cancer, medulloblastoma/glioblastoma, colorectal cancer (CRC), pancreatic cancer (PC), prostate cancer (PCa), and other cancer types associated with gastrointestinal or elementary canal and rhabdomyosarcoma [4, 41, 63–67]. These studies also demonstrated correlation between tumor types, response to treatment, and miR-1 expression. We have discussed the tumor-suppressive and immune-modulatory role of miR-1 in association with different cancers in coming sections.

2.1. Lung cancer

LC is a heterogeneous disease mainly includes two subtypes, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) and remains one of the major leading cause

of death globally [68, 69]. The outcomes of multiple studies from different LC models (cell line and mouse models) show that the downregulation of miR-1 is associated with LC [70–73]. Low expression of miR-1 was noticed in vinyl carbamate induced LC mice model compared to normal mice, and the expression was resumed when treated with the chemopreventive agent (indole-3-carbinol) [74]. In the case of NSCLC cell lines (A549), miR-1 directly targets phosphoinositide-3-kinase catalytic subunit alpha (PIK3CA) and inhibited the activation of downstream targets of the PI3K/AKT pathway (Figure 3) [75]. Overexpression of miR-1 in A549 cells showed decreased cell proliferation, migration, and invasion [75]. Another study showed that nearly 70% of NSCLC samples have low miR-1 and high PIK3CA expression, and low miR-1 patients have higher chances of lymph node metastasis and recurrence compared to moderate miR-1 and PIK3CA expression [76]. In addition, miR-1 overexpression inhibits LC growth via reducing metabolic mediators. Singh et al. have demonstrated that miR-1 plays a key role in LC metabolic reprogramming through regulating nuclear factor erythroid-2–related factor 2 (NRF2) [77].

Recently, Liu et al. showed that miR-1 downregulation increased the expression of FAM83A (family with sequence similarity 83, member A) in A549 and H1355 LC cells [70]. The 3-prime UTR of FAM83A has binding sites for miR-1 [70]. The miR-1 mediated downregulation of FAM83A inhibited the epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK), and choline kinase alpha (CHKA) signaling. Further, the inhibition of FAM83A decreases the LC cell growth, migration, and invasion [70]. In NSCLC microarray dataset analysis, miR-1 was reported as one of the most differentially expressed miRNAs that play an essential role in disease progression [71]. Interestingly, a recent report also showed the correlation of miR-1 with cigarette smoking and malignant transformation [78]. The continuous exposure of human normal bronchial epithelial cells (BEAS-2B) to cigarette smoke to transformed into malignant cells is associated with differential expression of miR-1. The miRNA sequencing data of LC and correlation of differentially expressed genes with smoke history identified miR-1 as a negatively regulated miRNA associated with epithelial to mesenchymal transformation (EMT). Overall, this study identifies miR-1 as a predictive biomarker for smoke-induced LC [78]. Computational studies also suggest that the downregulation of miR-1 is associated with lung squamous cell carcinoma (LUSC) [79]. This study showed the association of miR-1 with p53, cell-cycle regulation, and serine/threonine metabolism associated signaling pathways [79]. Long noncoding RNAs (lncRNAs) generally contain complementary sequences for various miRNAs, thus interacting with miRNAs through different types of interactions [80, 81]. The overexpression of the RNA component of mitochondrial RNA-processing endoribonuclease (RMRP) lncRNA has been associated with multiple cancers, including LC [82, 83]. Wang et al. reported that high expression of RMRP and low miR-1 is associated with advanced-stage NSCLC and poor overall survival [73]. Loss of RMRP or induction of miR-1 in LC cell lines reduced cell growth and motility with G0/G1 cell cycle arrest. It was also reported that miR-1 targets annexin-A2 (ANXA2), a highly overexpressed protein in NSCLC [73]. Knockdown of RMRP shows high expression of miR-1 and reduced levels of ANXA2; suggesting RMRP-miR-1 axis modulates LC growth through ANXA2, and thus provides a novel therapeutic target for LC therapies [73].

Drug resistance or resistance to chemotherapy is a significant problem associated with different LC treatments. Various miRNAs demonstrated their potential role in therapy resistance [84–86]. The prominent role of miR-1 towards the chemosensitivity of LC has also been reported by Hua et al. [87]. The miRNA expression analysis of cisplatin resistance NSCLC tissues showed a downregulation of miR-1 compared to sensitive patients, and the miR-1 expression is negatively associated with light chain 3 beta (LC3B, an autophagy marker) [87]. The resistant NSCLC cell lines showed low expression of p62 with an increased LC3B-II/LC3B-I ratio, and miR-1 overexpression decreased the LC3B-II/LC3B-I ratio. This study also identifies autophagy-related 3 (ATG3) as a target of miR-1. ATG3 was found to be upregulated in resistant NSCLC cell lines and positively correlated with LC3B expression and negatively with miR-1 expression (Figure 3) [87]. ATG3 is a ubiquitin-like enzyme working as an important component of the ubiquitination process that leads to the degradation and recycling process of cytoplasmic modules, phosphatidylethanolamine conjugation and autophagy regulation [88–90]. Interestingly, the 3'-UTR of ATG3 consists of miR-1 binding sites, and miR-1 regulates its expression. The upregulation of ATG3 eliminates the miR-1 oriented inhibition of autophagy in cisplatin-resistant NSCLC cells (A549 & H1299) [87]. This study validated the role of miR-1 in chemoresistance of NSCLC cell lines and tumor tissues and showed that miR-1 upregulation induces chemosensitization and apoptosis in resistant cell lines through LC3B/ATG3-mediated autophagy inhibition (Figure 3) [87]. Thus, providing the potential role of the miR-1-ATG3 axis in relieving LC chemoresistance.

Nearly half of the LC patients harbor "driver mutations" in EGFR, and thus EGFR-tyrosine kinase inhibitors (TKI) are recommended as the first choice of therapy, but due to the acquirement of mutations and other factors the patients develop therapy resistance [91–93]. In such patients, immunotherapy becomes one of the most imperative and leading therapeutic approaches that give promising outcomes [94, 95]. However, the lymphocyte infiltration and the expression of programmed death ligand-1 (PD-L1) rationalized immunotherapy efficacy prediction. The immune microenvironment of LC tumors still under investigation to identify novel predictors for immunotherapy. A recent study evaluated the correlation between miRNAs, lymphocyte infiltration, and EGRF-TKI (before and after acquiring resistance) in LC tumor tissues and cell line models [96]. The PCR-array analysis of LC tumor samples and cell lines identifies miR-1 as the most variable miR. This study showed the role of miR-1 in the modulation of tumor immune microenvironment (TIME) [96]. It inhibited the infiltration of $CD8^+$ T-cells and the production of C-C motif chemokine ligands (CCL5 and CCL10). Therefore, miR-1 plays a vital role in EGFR-TKI resistance and acts as a useful clinical predictor for the efficacy of immunotherapy [96]. Most of the studies (as discussed in previous sections) advocated the tumor suppressor activities of miR-1, however Kawana et al. suggests the additive role of miR-1 in EGFR-TKI resistance, thus adding a new paradigm to the future studies of miR-1, particularly in association with drug resistance and immunotherapy [96]. In addition to TIME, miR-1 plays a significant role in reprogramming normal fibroblasts to LC-associated fibroblasts through targeting CCL2 and VEGFA [97]. Overall, miR-1 studies in LC demonstrated that it acts as an essential regulator for pathogenesis, drug resistance, metastasis, and recurrence predictor, working as

a potential drug candidate and providing a suitable therapeutic approach for the treatment of LC.

2.2. Breast cancer

Breast cancer (BC) is one of the primary and leading causes of death in females [69]. BC patients showed high heterogeneity, and thus despite the availability of some therapeutic options for particular BC subtypes, limited therapeutic options are available for other subtypes like triple-negative phenotypes [98, 99]. Apart from protein-based therapeutic targets, miRNAs also play a major role in BC pathogenesis [100, 101]. In the case of triple-negative BC (TNBC) patients, the miR-1 expression is highly suppressed in TNBC cells relative to normal cells (MB-157) and cells derived from luminal subtypes [102]. The overexpression of miR-1 suppressed the cell migration, invasion, activation of ERK and MEK, and induced apoptosis (Figure 3). The induction of miR-1 also enhances the chemosensitivity of BC cells [102].

Mitochondrial retrogradation and nuclear crosstalk are associated with the development and pathogenesis of BC; thus, mitochondria provide different promising drug targets for BC [103–105]. The gene enrichment analysis using different TCGA tissue samples and microarray data generated a transcription factor-miRNA hub network that showed the upregulation of MYC-associated zinc finger proteins and downregulation of miR-1 is associated with poor overall survival and prognosis in BC [65]. This hub network regulates mitochondrial functioning and acts as a diagnostic biomarker and a therapeutic target [65].

The cardiotoxicity induced by anthracycline therapy in BC patients is a severe and frequent undesirable effect [106, 107]. The cardiac biomarkers and imaging are the main parameters to study the toxicity [106, 108]. Different RNA molecules, including miRNAs and small noncoding RNA, act as the biomarkers for cardiovascular diseases and toxicity, and miR-1 is a prominent one [109, 110]. Pereira et al. recently compiled the implication of miR-1 to access the cardiotoxicity of anthracycline treatment in BC patients [111]. They studied and compared the miRNA expression in the patient samples showing anthracycline-induced cardiotoxicity and no cardiotoxicity. The downregulation of miR-1 and some other miRNAs has been reported in epirubicin-induced cardiotoxicity and myocardial infarction compared to doxorubicin-induced cardiotoxicity [111]. It means that miR-1 plays a role in chemotherapy-associated cardiotoxicity of BC patients.

B-cell Lymphoma 2 (BCL2), an antiapoptotic protein, plays a regulatory role in different subtypes of BC and acts as a prognostic marker [112]. In the case of TNBC, BCL2 expression works as a poor prognostic factor [113]. BCL2 plays an important role in BC cell survival and apoptotic evasion, and therapeutic targeting of BCL2 improves the efficacy of endocrine therapy and decreases the tamoxifen-induced hyperplasia of the endometrium [114]. Thus, BCL2 targeting or using BCL2 specific small molecule inhibitors provides an attractive approach in BC therapies [114, 115]. Recently, Peng et al. showed that the miR-1 is downregulated in BC cells and patients samples compared to adjacent normal control [116]. Overexpression of miR-1 decreases the BC cell proliferation, invasion and induces apoptosis *in vitro* and *in vivo* through BCL2 downregulation (Figure 3). MiR-1 overexpression inhibited the tumor growth of BC cell xenografts in nude mice models.

Another exciting outcome of this study suggested that miR-1 sensitizes the BC cells towards chemotherapy (cisplatin and paclitaxel) [116]. Two independent studies reported the negative correlation between lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and miR-1 in BC cells and patient samples [117, 118]. The outcomes of these studies showed that MALAT1 promotes BC development, growth, metastasis, and EMT through miR-1 [117, 118]. Overexpression of miR-1 has been shown to decrease the expression of slug and MALAT1 with a corresponding decrease in tumor growth. Thus, these studies established miR-1 as a major tumor suppressor in BC, and targeted delivery of miR-1 may be a potential therapeutic approach for BC.

2.3. Colorectal cancer

Colorectal cancer (CRC) is the second leading cause of common cancer death in males and females in the United States [69]. Different molecules have been identified that promotes CRC development and progression, including transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), EGFR, B-Raf proto-oncogene serine/threonine kinase (BRAF), Kirsten rat sarcoma viral oncogene (KRAS), nicotinamide phosphoribosyltransferase (NAMPT), and SRY-box transcription factor 12 (SOX12) [119–121]. Apart from the known protein-coding genes, various miRNAs, including miR-1, also modulate CRC growth and development [122–125]. A recent study established the role of miR-1 in NAMPT and TGF-β signaling pathway that regulates the proliferation and growth of CRC cells [64]. NAMPT is a proinflammatory cytokine, and its overexpression is associated with the development of multiple cancers [126, 127]. Lv et al. reported that the 3-prime UTR of NAMPT has a putative binding site for miR-1, and TGF-β1 regulates the expression of miR-1 [64]. Overexpression of NAMPT leads to the increased expression of the TGF-β signaling pathway (Smad2-Smad3) and is associated with poor overall survival of CRC patients (Figure 3). The overexpression of miR-1 downregulated NAMPT and decreased the growth of CRC cells [64].

The *in silico* analysis of the CRC microarray dataset showed the downregulation of miR-1 in more than 90% of CRC cases [128]. Gene ontology analysis of CRC patients datasets showed positive results for transcription factor binding and RNA polymerase II-mediated regulations, and the hub gene analysis suggests miR-1 downregulation in the studied data sets of CRC [128]. Another interesting report has been shown that miR-1 inhibited the growth of CRC through VEGF downregulation [129]. The study results demonstrated that the miR-1 expression was downregulated in CRC tumor tissues and cell lines compared to normal tissue samples, and miR-1 expression is negatively associated with lymph node metastasis [129]. Overexpression of miR-1 inhibited the CRC cell migration and invasion, and miR-1 inhibited the expression and functional role of VEGF (Figure 3) [129]. This study reports VEGF as a direct target of miR-1 (as 3-prime UTR of VEGF consists of the miR-1 binding site) and provides the rationale of VEGF targeting through miR-1 for CRC therapies [129].

Two independent reports established the inhibitory role of miR-1 in aerobic glycolysis of CRC cells [130, 131]. Xu et al. using gain- or loss-of-function studies, established the role of miR-1 in glycolytic regulations of CRC [130]. Upregulation of miR-1 inhibited the

aerobic glycolysis (Warburg effect) and lactate production in CRC cells through Smad3 and hypoxia-inducible factor 1 subunit alpha (HIF1α). MiR-1 targets HIF1α and decreases the expression of hexokinase 2 (HK2) and monocarboxylate transporter 4 (MCT4). Activated Smad3 interacts with HIF1α, however, miR-1 overexpression did not allow this interaction. It was demonstrated that miR-1 acts via Smad3/HIF1α axis in CRC and overexpression of miR-1 decreases the *in vivo* CRC growth through aerobic glycolysis modulation [130]. Similarly, Taniguchi et al. showed that downregulation of miR-1 induces the Warburg effect in CRC through pyruvate kinase in the muscle (PKM) and polypyrimidine tract-binding protein 1 (PTBP1) [131]. The overexpression of miR-1 induces class switching of PKM isoform from PKM2 to PKM1 by decreasing the expression of PTBP1 and reduces tumor growth and autophagy [131]. Overall, these studies showed that the downregulation of miR-1 in CRC has a diagnostic utilization, and overexpression of miR-1 is a potential therapeutic strategy for CRC patients.

2.4. Gastric cancer

Gastric cancer (GC) is also a leading cause of cancer-related deaths [69]. Due to the late diagnosis and high metastasis, few therapies are available for the treatment of GC. Multiple studies suggested that aberrant expression of miRNAs contributes towards the tumorigenesis of GC [132, 133]. Among various miRNA, the miR-1 expression has been found downregulated in GC [41, 134]. It was reported that low expression of miR-1 is associated with poor overall survival compared to higher expression in GC patients [134]. MiR-1 overexpression decreased the expression of VEGF and endothelin 1 in GC cells and inhibited cell proliferation and migration [134]. Another recent report showed that miR-1 inhibited the expression of VEGF, sorcin, and MMP-7 and decreases the invasion of GC cells [135]. Therefore, miR-1 regulates the angiogenic factor of GC and acts as a tumor suppressor.

The miR-1 expression also plays a role in developing drug resistance in GC cells [136]. It was shown that miR-1 is highly downregulated in resistant GC cells, and sorcin is upregulated [136]. In resistant GC cells, overexpression of miR-1 sensitizes the cells towards ADM/cisplatin and increases the apoptosis through sorcin targeting [136]. Stanniocalcin 2 (STC2) and MET proto-oncogene (MET) is the other target of miR-1 that regulates GC growth [45, 137]. Overexpression of miR-1 downregulated the expression of MET and STC2, decreases the GC cell migration and correlated with the tumor regression [45, 137]. Additionally, a recent report suggested the role of miR-1 in the metabolism of GC cells [66]. It has been shown that the expression of LINC00242 and glucose-6-phosphate dehydrogenase (G6PD) is very high in GC tissues and cell lines. Silencing of G6PD or LINC00242 inhibited the aerobic glycolysis of GC cells and upregulated the expression of miR-1. LINC00242 regulates the miR-1/G6PD axis in GC cells and provides a novel therapy target [66].

2.5. Liver cancer

Liver cancer or hepatocellular carcinoma (HCC) is one of the major cancers of the gastrointestinal tract. The tumor-suppressive role of miR-1 was demonstrated for the first time in liver cancer [138]. Epigenetic modifications like hypermethylation of CpG islands

were also reported to downregulate the expression of miR-1 in HCC cell lines [138]. DNA methyltransferase 1 (DNMT1) regulated the methylation pattern of *MIR-1* gene and showed reduced expression of miR-1 in HCC compared to matching control. Overexpression of miR-1 decreased the cell growth and clonogenic properties of HCC cells. It was shown that miR-1 performs antitumorigenic activity through FOXP1 and hepatocyte growth factor receptor (cMET) inhibition, and these molecules possess miR-1 binding sites in their 3′-UTR [138]. These observations encourage the combination of epigenetic drugs with miR-1 to treat HCC and other cancers where miR-1 expression is regulated through epigenetic pathways. Added to the antitumorigenic potential of miR-1 in HCC, one more recent study reported the downregulation of miR-1 in HCC cells compared to normal cells and suggested SOX9 as a target of miR-1 [139]. Overexpression of miR-1 inhibited HCC cell growth and decreased *in vivo* tumor growth through SOX9 inhibition [139].

Sorafenib (a multi tyrosine kinase inhibitor) is used as standard therapy for HCC, but its application was limited by therapy resistance [140]. It was reported that PD-L1 plays a vital role in drug resistance and immune evasion of various tumors [141, 142]. A recent study by Li et al. demonstrates the overexpression of PD-L1 in sorafenib-resistant HCC cells and depletion of PD-L1 suppressed the clonogenic potential, invasion, and drug resistance *in vitro* and *in vivo* studies [143]. Mechanistic studies showed a negative correlation between PD-L1 and miR-1 expression in sorafenib-resistant HCC cells. PD-L1 was identified as a direct target of miR-1 and showed that nuclear factor erythroid 2-related factor 2 (NRF2) expression is increased in resistance cell lines that downregulates miR-1 expression. Thus, NRF2/miR-1/PD-L1 axis contributes to the sorafenib resistance in HCC, and overexpression of miR-1 induces tumor inhibitory activities through PD-L1 downregulation [143]. This study suggests the implication of miR-1 in PD-L1 regulation and provided a novel therapeutic axis to deal with drug resistance, including immunotherapy.

Interestingly, apart from human beings, a recent report suggested the implications of miR-1 expression in canine HCC [144]. Canine HCC is a commonly diagnosed primary hepatic tumor in dogs [144, 145]. The outcomes of the study reported by Lai et al. showed that downregulation of miR-1 is associated with canine HCC, and identifies cMET as a target of miR-1 [144]. The comparison of high versus intermediate proliferating canine HCC cells showed higher cMET expression both at gene and protein level and was found directly associated with miR-1 expression [144]. Low miR-1 and high cMET conditions are associated with canine HCC cell proliferation and provided a rationale for the future exploration of the miR-1/cMET axis for therapy development.

2.6. Other cancers

Apart from the above-discussed cancers and targets, miR-1 also plays a tumor suppressive role in other cancers, including pancreatic, medulloblastoma, and prostate cancer with multiple targets as summarized in (Table 1) [146–148]. The downregulation of miR-1 also contributes to the development of pancreatic ductal adenocarcinoma (PDAC) [148]. The microarray analysis of PDAC tissues, *in situ* hybridization, and miRNA profiling of patient serum, suggested that miR-1 is downregulated in PDAC. The low miR-1 and high miR-214 expression are associated with poor survival of PDAC patients [148]. The

outcomes of the study suggested that miR-1 plays an important role in carcinogenesis and, along with miR-214, stood as a prognosis biomarker for PDAC. In PCa, a significant downregulation of miR-1 was reported in recurrent tissues compared to non-recurrent ones and acts as a predictive marker for PCa recurrence [149]. High expression of MALAT1 and low expression of miR-1 were noticed in PCa cell lines and tumor tissues [149]. MALAT1 works like a sponge for miR-1, and knockdown of MALAT1 induces apoptosis in androgen negative PCa cells. Mechanistic studies showed that miR-1 targets KRAS in PCa cells, and MALAT1 increases KRAS expression by competing with miR-1 [149]. Upregulation of miR-1 in androgen negative PC cells inhibited the cell proliferation, migration, and induced apoptosis through KRAS targeting. Thus, the MALAT1/miR-1 axis acts as a potential therapeutic target for treating recurrent or castration-resistant PCa [149]. EGFR signaling modulates bone metastasis of multiple cancers, including PCa [147, 150]. Translocation of EGFR into nucleus downregulates miR-1 expression that promotes PCa bone metastasis. Additionally, miR-1 expression is negatively correlated with the expression of EGFR and twist family BHLH transcription factor 1 (TWIST1) in PCa tumor tissues [147]. The findings of this study demonstrated that EGFR works as a repressor for miR-1 transcription, whereas it activates TWIST1 that promotes PCa bone metastasis and restricts the antitumorigenic activity of miR-1 [147].

The microarray analysis and integrated miRNA expression studies showed the downregulation of miR-1 in esophageal squamous cell carcinoma (ESCC) [151]. In situ hybridization and miRNA-mRNA network studies in ESCC cells and tumor tissues showed the downregulation of miR-1 is associated with different pathological parameters like lymph node metastasis, migration, invasion, and poor overall survival. Overexpression of miR-1 facilitates apoptosis and inhibits the invasion of ESCC cells through downregulation of fibronectin 1 (FN1), suggesting the implication of the miR-1/FN1 axis for therapy development [151]. Bladder cancer cells and tumor tissues showed low miR-1 and high C-C motif chemokine ligand 2 compared to normal tissues (CCL2) [152]. Induction of miR-1 reduced the cell proliferation and induced apoptosis through downregulation of CCL2. Since miR-1 has a binding site in 3’UTR of CCL2, suggesting that the anticancer activity of miR-1 in bladder cancer is associated with CCL2 targeting [152].

Downregulation of miR-1 has also been reported in the case of head and neck squamous cell carcinoma (HNSCC) tumor tissues [153]. The restoration of miR-1 expression decreases the aggressiveness of HNSCC cells. Combinatorial analysis of cancer pathways showed that miR-1 modulates ECM-receptor, FAK, and MAPK signaling pathways. Among different selected molecules, EGFR and cMET were presented as a direct target of miR-1 and their (EGFR/cMET) overexpression was reported in HNSCC tumor tissues [153]. MiR-1 overexpression decreases the expression of EGFR and cMET that further provides a preclinical rationale to target these oncogenic regulators through miR-1. HOX transcript antisense RNA (HOTAIR, a lncRNA) and Yin Yang 1 (YY1) are also involved in the tumorigenesis of medulloblastoma [146, 154]. Low expression of miR-1 and high expression of HOTAIR and YY1 were noticed in medulloblastoma cell lines and tumor tissues. It was shown that HOTAIR negatively regulates the miR-1 expression, and YY1 has a putative binding site for miR-1; thus, HOTAIR increases the expression of YY1. The knockdown of HOTAIR or overexpression of miR-1 decreased the tumor growth of medulloblastoma

cell lines and reduced EMT markers (vimentin, fibronectin), and induces apoptosis [146]. Overall, the discussion of miR-1 associated cancer pathways and prominent cancer drug targets of multiple cancers strengthens our understanding of the consistent tumor suppressor nature of this miRNA. Future investigation may lead to a better understanding of miR-1 modulated targets that may augment the development of different therapeutic strategies for cancers.

3. MiR-1 and immunity

It is now well established that miRNAs play a key regulatory role in multiple physiological processes, including immune responses, and the number of miRNAs implicated in immunomodulation is continuously increasing [155, 156]. Local or innate immune response has emerged as an essential part of different aspects of cancer development, such as inflammation, metastasis, angiogenesis, modulation of TIME, and chemo-/immunotherapy response [157–159]. Tumors are not only infiltered by molecules of the innate or adaptive immune system, but the cells of both arms of the immune system constitute the tumor microenvironment [160–162]. Based on the fine-tuning of the innate and adaptive immune system, immunity can act as an anti- or pro-tumorigenic factor [162]. One such component that regulates the nature of the immune response is miRNAs, and among them, miR-1 has been known to regulate production and release of chemokines/cytokines, expression of costimulatory molecules, miRNA shuttling through exosomes, regulation of immune homeostasis, inflammation, and cancer immunotherapy response [56, 143, 163–170].

The expression status of miR-1 has been found to determine immunotherapy response as PD-L1 is a direct target of it [143]. It was demonstrated that sorafenib-resistance cancer cells have higher expression of PD-L1 and low miR-1 [143]. It means that low miR-1 is a predictive factor for immunotherapy response, and miR-1 combination therapies with standard chemotherapy or tyrosine kinase inhibitor could be novel approaches to treat such cancers. It was reported in LC that miR-1 expression determines the sensitivity of EGFR-TKI as it regulates the lymphocyte infiltration, monocyte migration, and the production of CCL-5/−10 chemokines [96]. Few studies are available that projected the role of miR-1 directly in tumor immunity, but multiple studies are available that showed that miR-1 modulates the immune-related pathways in various diseases like cardiac injuries and lung diseases [171, 172]. Interestingly similar pathways are found dysregulated in various cancers, thus putting forward the implications of miR-1 in tumor-immunity. On this line, we discussed some important immune regulation studies of miR-1.

Interestingly, miR-1 has been shown to modulate T-helper type 2 cell (Th2)-mediated inflammatory diseases like asthma [171]. VEGF is a key mediator of Th2 mediated inflammation in the lung and other diseases [173, 174]. It was shown that overexpression of VEGF in lung epithelium cells decreased the expression of miR-1, and this was recapitulated in animal models of Th2 inflammation. The external delivery of miR-1 through the intranasal route inhibited the inflammatory response to house dust, ovalbumin, and IL-13. VEGF inhibition blocks the Th2-mediated inflammatory response, and the response was restored through miR-1 inhibition. Pull-down assays of Argonaute showed that myeloproliferative leukemia protein (MPL) was a direct target of miR-1 [171].

During Th2 oriented inflammation, VEGF modulates the expression of MPL through miR-1. Knockdown of MPL leads to inhibit Th2-mediated inflammation, decreases mucin production, and expression of P-selectin [171]. Apart from these observations in Th2 animal models, similar outcomes were noticed in human primary endothelial cells (HUVECs), which suggested that miR-1 might play a crucial immunological role in different lung diseases, including LC [171]. The P-selectin is a vital adhesion molecule present on lung epithelium cells, and aberrant expression is associated with multiple malignancies, angiogenesis, and modulation of the CXCL12-CXCR4 axis [175].

P-selectin recruits T cells and eosinophils to lung epithelium and augments the inflammation through Th2 cytokines [176]. Additional studies are required to describe the functional relevance of miR-1, VEGF, MPL, and P-selectin in regulating Th2 response in inflammation-associated diseases, including cancer. A similar observation was reported recently by Korde et al. in asthma and chronic rhinosinusitis that the overexpression of miR-1 in lung endothelium decreased the trafficking of eosinophils or IL-13 oriented inflammation in murine models [172]. The miR-1 enrolled thrombopoietin receptor and P-selectin to miRNA RISC complex for degradation and decreased the expression of these genes in epithelial cells [172]. Jiang et al. recently reported the role of miR-1 in inflammation and atherosclerosis [177]. It was demonstrated that miR-1 regulates the activation of NF-kB that activates the expression of various proinflammatory cytokines and immune cells [177]. The demonstrated functional role of miR-1 and VEGF in asthmatic lung inflammation, mucin regulation, NF-kB regulation, and T-cell recruitment suggested the implications of the miR-1/VEGF axis in other diseases such as cancer, where these molecules play a crucial role in disease progression and therapy development.

4. Concluding remarks and future perspectives

Collecting outlines of multiple studies show the key developmental and tumor-suppressive roles of miR-1. The miR-1 can regulate the expression of various key regulatory targets at the post-transcriptional level that manifests the pathogenesis of various human disorders. The expression of miR-1 plays a particular role in tumor growth, therapy response, and immune response. The initial studies demonstrated the development specific role of miR-1 in skeleton muscle and cardiomyocytes, whereas recent studies suggested the prevalent role of miR-1 in inflammatory diseases, various cancers, and other pathological conditions [40, 41, 171, 172]. The functional diversity of miR-1 can be realized through its varied targets (Figure 3).

Several associated fields need detailed future investigations to continue the progress of miR-1 implications in cancer research and therapy development. One such field of miR-1 is a detailed study of tumor-associated immune functions that needs the improved implications of high-throughput RNA sequencing cross-linked with immunoprecipitation [178, 179]. In most cases, miR-1 or other miRNAs facilitate their functional activities at the protein level that make immune target identification particularly difficult through transcriptomic data. The development of better understanding and selective dispensation of miR-1 clusters in the immune system is highly desired. The promising efforts for *in vivo* delivery of miR-1 mimics to combat inflammation [171, 172] further opened the exciting options of

miR-1 mediated therapeutic targeting of various malignancies. The therapeutic targeting of various cancers through miR-1 needs formulation optimization and development of delivery methods, that will open a window to utilize this molecule in therapy development.

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Abbreviations

EGFR	Epidermal growth factor receptor
NSCLC	Non-small cell lung cancer
SCLC	small cell lung cancer
KRAS	Kirsten rat sarcoma viral oncogene homolog
TK	Tyrosine kinases
PARP	ADP-ribose polymerase
STC2	Stanniocalcin 2
G6PD	glucose-6-phosphate dehydrogenase
ACT	Adoptive cell transfer
VEGF	Vascular endothelial growth factor
miRNAs	microRNAs
siRNA	small interfering RNA
RISC	RNA-induced silencing complex
KLF4	Kruppel-like factor 4
HSP60	heat shock protein 60
HAND2	heart and neural crest derivatives expressed 2
STC2	stanniocalcin 2
TGF-β	transforming growth factor-beta
MyoD	myoblast determination protein 1
Mef2	myocyte enhancer factor-2

cMET	hepatocyte growth factor receptor
PIK3CA	phosphoinositide-3-kinase catalytic subunit alpha
FAM83A	family with sequence similarity 83 member A
MAPK	mitogen-activated protein kinase
CHKA	choline kinase alpha
FN1	Fibronectin 1
lncRNAs	Long noncoding RNAs
RMRP	RNA-processing endoribonuclease
ANXA2	targets annexin-A2
ATG3	autophagy related 3
LC3B	light chain 3 beta
PKM	pyruvate kinase in muscle
PTBP1	polypyrimidine tract-binding protein 1
NRF2	nuclear factor erythroid 2-related factor 2
HIF1α	hypoxia inducible factor 1 subunit alpha
HK2	hexokinase 2
MCT4	monocarboxylate transporter 4
SOX12	SRY-box transcription factor 12
YY1	Yin Yang 1
BRAF	B-Raf proto-oncogene serine/threonine kinase
CRC	Colorectal cancer
MALAT1	metastasis associated lung adenocarcinoma transcript 1
CCL	C-C motif chemokine ligands

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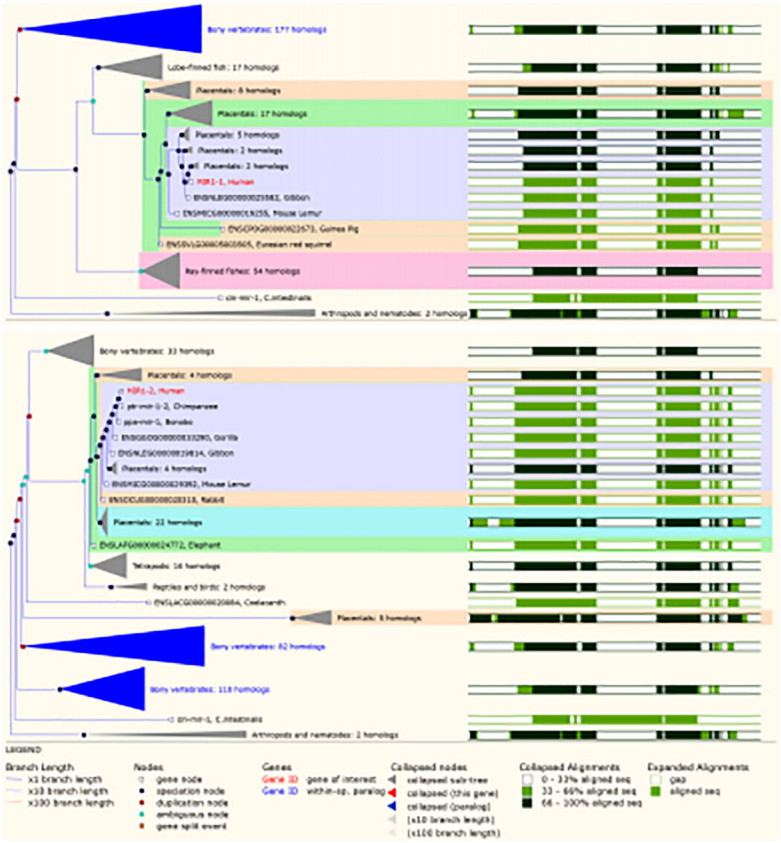

Figure 1:

Gene tree representing the alignment of human *MIR-1–1* and *MIR-1–2* gene with other species. The gene tree analysis showed the conserved pattern of miR-1 across the species. Gene tree was created using Ensembl genome database (Ensemble archives103) [180].

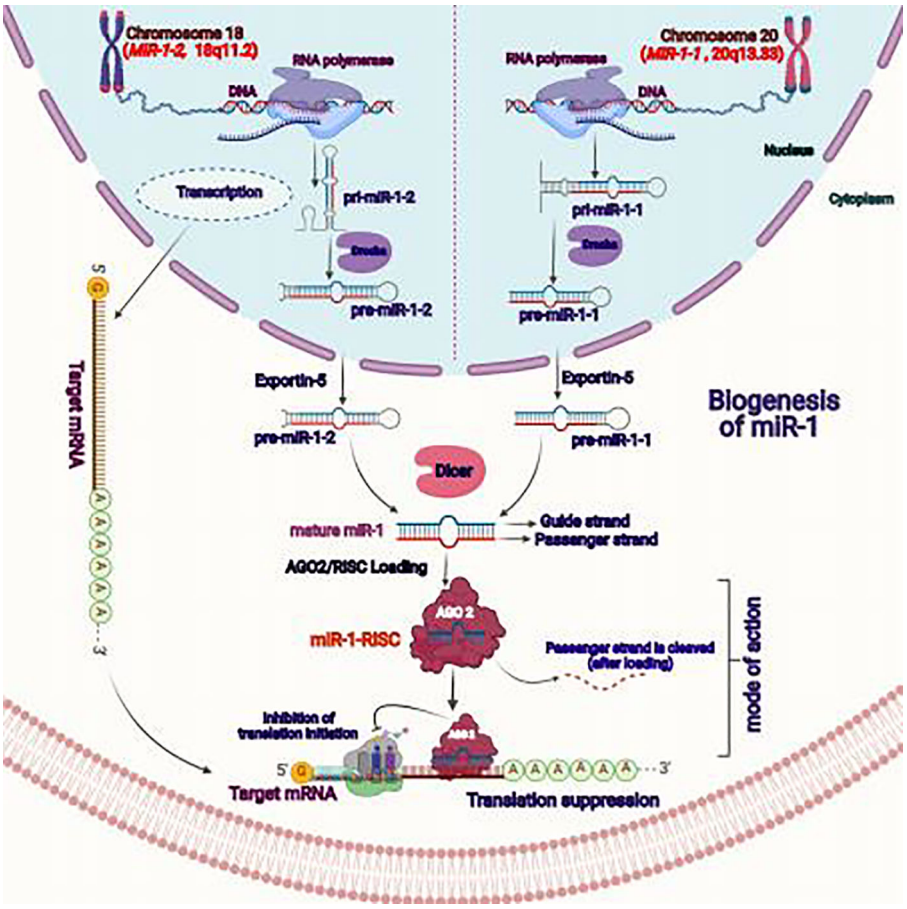

Figure 2: Mechanism of miR-1 biogenesis and common mechanism of action.

In case of humans, two discrete genes, MIR1–1 located on 20q13.333 and MIR1–2 located on 18q11.2 loci encode for a single mature miR-1. The initial stem loop or primary miR-1–1/miR-1–2 (pri-miR-1–1/pri-miR-1–2) were transcribed by RNA-polymerase II and DROSHA processed them into pre-miR-1–1 or pre-miR-1–2. The pre-miR-1 sequences then transported from the nucleus through exportin-5. Reaching out form the nucleus to cytoplasm, the pre-miR-1 sequences were processed by DICER and a single mature miR-1 was generated from both types of pre-sequences. The mature miR-1 was loaded to AGO2 that form miR-1-RISC complex for specific gene targeting or translation inhibition.

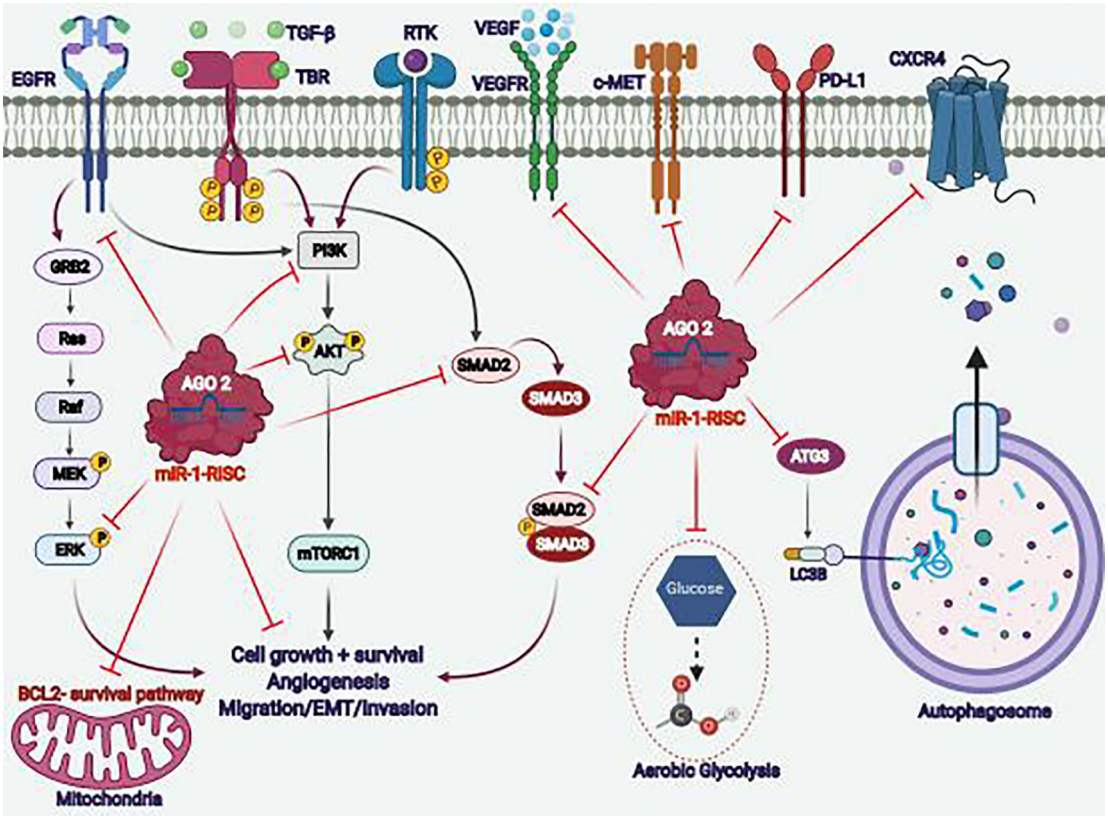

Figure 3: Schematic illustrations for miR-1 modulated cancer associated signaling pathways and other targets.

MiR-1 downregulation is implicated in the various oncogenic signaling pathways, and overexpression of miR-1 or miR-1-RISC complex decreases/inhibited the activation of transcription factors or other protein molecules in multiple pathways associated with cancer cell proliferation, cell-growth, survival, angiogenesis, metastasis, metabolism (aerobic glycolysis), and autophagy mediated networks.

Table 1:

Cancer associated targets of miR-1 and related functional role.

Name of target	Function	Type of Cancer	Reference
ATG3	-chemosensitization -regulates autophagy -induces apoptosis	NSCLC	[87]
CDC42	-migration & invasion	BC	[118]
PD-1/PD-L1	-immune suppression -drug resistance	HCC, LC	[96, 143]
CCL2	-suppressing the proliferation & invasion	Bladder cancer	[152]
VEGF	-fibroblast reprogramming -Th2 mediated inflammation -reduces tumor growth -decreases cell migration & invasion	LC, CRC, GC	[97, 129, 134, 135, 171]
Bcl-2	-decreases cell survival -chemosensitization -inhibited tumor growth -radioresistance	BC, CRC	[116, 181, 182]
E-Cadherin	-metastasis -radioresistance	BC, CRC, Cervical cancer	[116, 181, 183]
Slug	-cell growth & development -metastasis -EMT	BC, LC	[117, 184]
EVI-1	-inhibit cell proliferation -promote apoptosis -decreases EMT -reduced tumor growth	BC	[185]
CXCL12	-cell invasion -metastasis	Thyroid carcinogenesis, BC, LC	[186, 187]
CXCR4	-regulate SDF-1 biogenesis in cancer-associated fibroblasts -metastasis	BC, LC	[187, 188]
EGFR	-angiogenesis -inhibit proliferation and invasion of tumor cells.	HNSCC, Glioblastoma, Ovarian cancer, PCa	[153, 189, 190]
c-MET	-suppress growth & proliferation -decreases MCL1	Ovarian cancer, Osteosarcoma, HNSCC, PCa	[153, 191–194]
G6PD	-suppress cancer development and progression	Cervical cancer	[195]
CDK4	-decreases tumor growth and metastasis -G1 cell-cycle arrest.	GC, BC, clear cell renal cell carcinoma	[196, 197]
ANXA2	-decreases cell growth and migration -reduces angiogenesis and invasion -G0/G1 cell cycle arrest -target stem cell features	NSCLC, glioblastoma	[73, 198]
AKT	-inflammation -cell growth	CRC, PCa	[194, 199]
PI3K	-inflammation -cell growth	CRC	[199]
HDAC6, HNF4α	-decreases mucin expression -regulate bile reflexes and metaplasia	Gastro-intestinal cancer/ metaplasia	[200]