

An Overview on the Pathophysiological Roles of microRNA- 802: a Literature Review

Maryam Eini ¹, Jafar Kiani ², Elahe Seyed Hosseini ³, Marziyeh Alizadeh Zarei ³,
Sepideh Parsi ⁴, Mahmood Barati ¹, Golnaz Bahramali ⁵, Arshad Hosseini ^{1,*}

¹ Department of Biotechnology, Faculty of Allied Medicine, Iran University of Medical Science (IUMS), Tehran, Iran; eini.mry@gmail.com (M.E.);

² Department of Molecular Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran; kiani_jafa@yahoo.com (J.K.);

³ Gametogenesis Research Center, Kashan University of Medical Science, Kashan, Iran; marziyehalizadeh91@yahoo.com (M.A.Z.);

⁴ Department of Biochemistry and molecular pharmacology, University of Massachusetts medical school Worcester MA USA; s.parsi2005@gmail.com (S.P.);

⁵ Pasteur Institute of Iran, Tehran, Iran; gbahramali@gmail.com (G.B.);

* Correspondence: hoseini.a@iums.ac.ir (A.H.)

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Abstract: Over the last two decades, microRNAs (miRNAs) have emerged as a novel class of small non-coding RNAs that fine-tune the expression of various target genes at a post-transcriptional level. Recent studies have highlighted the functional roles of miR-802 in different pathological and physiological conditions. By means of different molecular techniques, including high throughput and gene silencing ones, miR-802 aberrant expression and some of its targets and mechanisms of action have been determined in obesity, glucose metabolism, different types of cancers, Down syndrome, nephropathy, and immune system-mediated conditions. Herein, we review the current knowledge about promising applications of miR-802 in human diseases as biomarkers and therapeutic targets.

Keywords: micro RNA; miR-802; cancer; Down syndrome; obesity; glucose intolerance; diabetes Mellitus; small intestine; nephropathy; kidney.

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1. Introduction

MicroRNAs (miRNAs) are a large family of highly conserved small non-coding RNA (~22 nt) molecules. Since their discovery in 1993, miRNAs have evoked a great deal of interest due to their essential roles in various aspects of biological processes [1]. Approximately 17,000 miRNAs have been identified in different species, each regulating the expression of dozens of target genes [2]. Through a complex biogenesis process, miRNAs regulate the expression of at least 60% of human protein-coding genes [3-5]. MiRNAs are master regulators in modulating normal physiological conditions, including energy metabolism, tissue remodeling, cell differentiation, and immunity, whereas their aberrant expression is linked with diverse pathological conditions [6-10]. MicroRNA-802 (miR-802), a recently identified miRNA located on chromosome 21, is involved in a number of human diseases [11-13]. Due to its location on chromosome 21, earlier studies have been investigating the role of MiR-802 in inherited genetic disease, down syndrome [14]. Soon after that, the physiological effect of MiR-802 on overexpression of renal outer medullary potassium (ROMK) channels on the

surface of the distal nephron was unveiled [15]. Two other recent important eras that emerging roles of MiR-802 have been investigated in them are glucose metabolism and cancer [16,17]. The present article reviews the functions of miR-802 in the context of metabolism, cancer, Down syndrome, and other pathophysiological conditions (Figure 1).

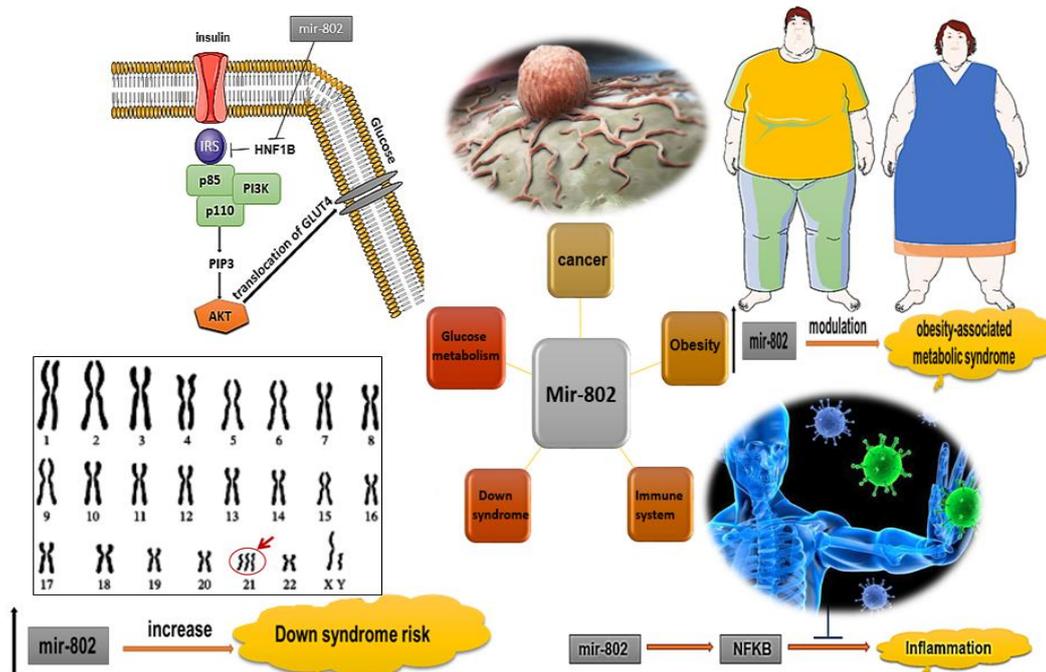


Figure 1. Pathophysiological roles of microRNA-802 in different human diseases.

2. Pathophysiological Role of miR-802 in Metabolism

Compelling evidence has illustrated that dysregulated miRNAs are critically associated with obesity and some of its most important related conditions. According to previous studies, overexpression of miR-143, miR-181, miR-103, and miR-107 is associated with obesity-induced insulin resistance [18-20]. However, some confirmations in recent studies have demonstrated the strong role of a novel biomarker in glucose metabolism disorders is miR-802. In a study conducted by the Kornfeld group in 2013 that was published in Nature, it has been shown that overexpression of miR-802 is even more pronounced than previously reported miRNAs in the liver of mice homozygous for diabetes (db) mutation of the leptin receptor (Leprdb/db) and high-fat diet (HFD)- fed mice versus wild-type controls. This overexpression which has been existed in some other tissues, including white adipose tissue, kidney, and pancreatic islets, impairs glucose metabolism arising from the reduction of insulin's ability to phosphorylate Serine/Threonine Kinase AKT which acts as the central signaling node for insulin function. In addition, hepatocyte nuclear factor 1beta (Hnf1b) mRNA has been confirmed as one of the miR-802 targets that have the potential to control overexpression of cytokine signaling Socs1 and Socs3, which are known as insulin resistance mediators [16].

Also, results from another study recently published in Nature in 2020 showed overexpression of miR-802 in the obese mouse models pancreatic islets, which damages insulin production and secretion by downregulation of NeuroD1 and Fzd5 [21]. Another study demonstrates that in Argonaute 2 (Ago2) knock out and HFD- fed mice, Ago2 regulates miR-802 expression and miR103/107 and miR-148a/152. all of this miRs would have important roles in metabolic conditions, which shed more light on the functions of miR-802 and RNA silencing in metabolic homeostasis [22].

In the case of miR-802, circulating miR-802 has been recognized as a type 2 diabetes biomarker [11]. Another study that highlights miR-802 as a possible biomarker for type 2 diabetes was an *in silico* investigation performed on expressed sequence tags (EST) of human mRNAs belonging to type-2 diabetes mellitus cases retrieved from the data of the national center for biotechnology information (NCBI). Alignment of ESTs against human mature miRNA sequences extracted from mirbase, identified hsa-miR-802-5p as matched miRNA to EST sequences that clearly suggest the probable clinical relevance of miR-802 and type-2 diabetes [23]. Moreover, induced overexpression of miR-802 raises the production of lipid peroxidation and reactive oxygen species through JNK and p38MAPK pathways activation, which leads to insulin resistance [24,25]. On the other hand, inhibition of miR-802 causes human Prkaa1 overexpression and a higher level of phosphorylated AMPK, which decreases hepatic lipogenesis [26]. Furthermore, it has been demonstrated that Farnesoid X receptor (FXR) and FXR-induced small heterodimer partner (SHP) are possible regulators of miR-802, and defective FXR-SHP in obesity, promotes overexpression of miR-802, insulin resistance and fatty liver [27].

Another interesting study has investigated the role of miR-802 in cardiac myocytes. It has been demonstrated that in exosomes derived from hypertrophic adipocytes, miR-802 is overexpressed. Exposure of these exosomes to neonatal rat ventricular myocytes resulted in down-regulation of heat shock protein 60 (HSP60) and, subsequently, overexpression of CHOP (a marker of the unfolded protein response) enhanced oxidative stress, and cardiac insulin resistance [28]. Generally, it seems that studying miR-802 in the glucose metabolism disorders era is growing, which could result in bringing up this microRNA as a novel and promising therapeutic target.

3. Pathophysiological Role of miR-802 in Cancer

The potential role of miR-802 in cancer was initially demonstrated in 2013 by examining miR-802 expression level and its effects on osteosarcoma tumor tissues and related cell lines. miR-802 expression is upregulated in osteosarcoma tumor tissue from patients [17]. Testing this miRNA *in vitro* showed that increased expression of miR-802 induces proliferation of osteosarcoma cells by targeting p27, a cell-cycle regulator [17,29]. Investigation on the role of miR-802 has been followed in other types of cancers, including lung, liver, breast, prostate, gastric, ovarian cancers, and so forth [30]. It is also identified as signature microRNA in patients who are at risk of dysplasia and cancer originating from Barrett esophagus [31]. MiR-802 targets, results, and other information from these studies are summarized in table 1 (Table 1). A similar result to osteosarcoma was reported for lung cancer, indicating miR-802 overexpression in lung cancer tissues [32]. In the *in vitro* examinations, downregulation of tumor suppressor menin (MEN1) by miR-802 was confirmed by changes in the expression level of involved genes in downstream signaling of menin, resulting in cell proliferation in lung cancer cell lines [32]. Contrary to the overexpression of miR802 in Qing Wang *et al.*'s study, another group found that this miRNA is downregulated in serum samples of mice, which are exposed to ambient fine particulate matter (PM_{2.5}) for a long time. This is linked to increased lung cancer mortality, Rnd3 expression levels, and dysregulation of the actin cytoskeleton [33]. In regard to breast cancer, downregulation of miR-802 is reported [34]. In addition, it is demonstrated that induced overexpression of miR-802 decreased the level of Forkhead box protein M1 (FoxM1) and inhibited the proliferation in Breast cancer cell lines and nude mice [35]. Besides, in the GSE136149 dataset, circulating miR-802-5p, as well as miR-194-5p and

brain MEF2C, have been reported as a biomarker of breast cancer brain metastasis in mus musculus [36].

Epithelial-Mesenchymal Transition (EMT) is the other studied effect of miR-802, which has been investigated in prostate cancer cell lines and xenograft models. MiR-802, with tumor suppressor properties, directly targets Flotilin2 (*Flot2*) which has an important role in malignancies. Downregulation of *Flot2* could result in suppression of EMT, migration, and invasion in prostate cancer cell lines [37]. Besides, it has been shown that mice injected with miR-802 overexpressing DU145 (a human prostate cancer cell line) cells have markedly slower tumor growth compared with control mice ($P < 0.05$) [37].

In another study, two different mouse models of liver cancer, induced by AKT/Ras or *c-Myc* oncogenes overexpression, exhibited significant downregulation of miR-802 and co-injection of precursor plasmid of this miRNA with oncogenes resulted in lower tumor burden in *c-Myc* induced liver cancer mouse models [38].

MiR-802 is upregulated in hepatocellular carcinomas (HCC) that decreases ZNF521 expression level, which is a multi-functional transcription co-factor consisting of a tumor suppressor gene and 30 zinc fingers. However, transfection of cells with ZNF521 overexpression vectors resulted in inhibition of colony formation, cell proliferation, and cell viability by transcriptional inhibition of Runx2 [39].

Tongue squamous cell carcinoma is the other studied cancer that displayed the tumor-suppressive role of miR-802 targeting *RAB23* [40].

In two studies conducted on human cervical cancer, cell proliferation and EMT were inhibited by miR-802 through downregulating serine/arginine-rich splicing factor 9 (*SRSF9*) and basic transcription factor 3 (BTF3), respectively [41,42]. MiR-802 involves the cervical cancer cells' progression and metastasis by targeting the MYLIP gene [43].

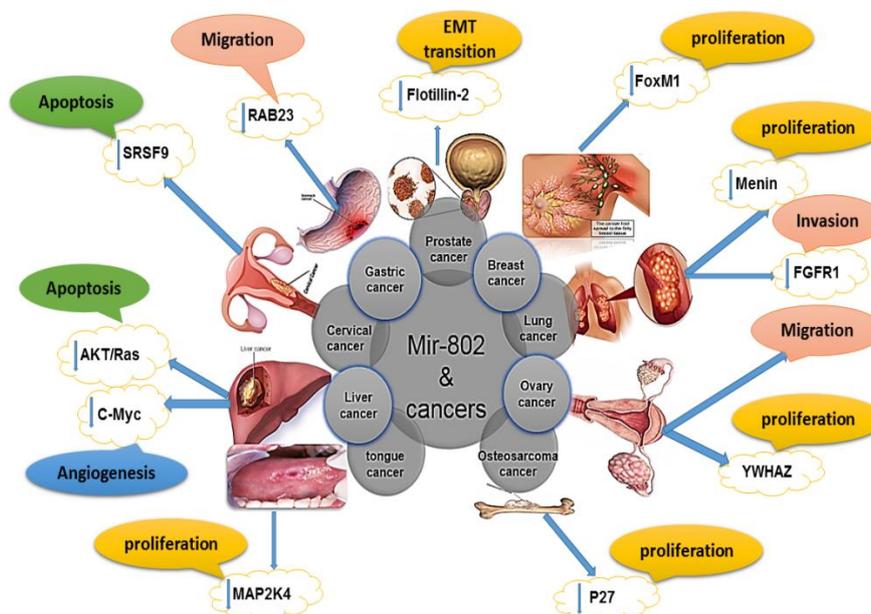


Figure 2. The effect of mir-802 in different human cancers.

Since microRNAs can be regulated by long non-coding RNAs (lncRNAs), it is reported that lncRNA MIR155HG can negatively regulate miR-802, resulting in pancreatic cancer progression, whereas silencing MIR155HG could revert the result [44]. The role of miR-802 in early pancreatitis as well as pancreatic carcinogenesis through suppressing acinar-to-ductal reprogramming has been reported as well [45].

In ovarian cancer, the miR-802 is downregulated in both cancer cell lines and tissues compared to normal controls. Importantly, overexpression of miR-802 could significantly inhibit the invasive properties and induce apoptosis in the ovarian cell via targeting 14-3-3 protein zeta/delta (YWHAZ) protein [46]. Colorectal cancer (CRC) is the other malignancy that miR-802 is investigated. A similar result from two studies on colorectal cancer tissues and cell lines demonstrated that miR-802 and Ras-associated nucleus (RAN) are downregulated and upregulated, respectively. Ran regulates the EGFR expression and activates AKT and ERK signaling pathways, especially in proliferation and metastasis. It has been shown that induced overexpression of miR-802 suppresses colorectal cancer cell viability, as well as invasion by downregulating RAN directly [47,48]. All the reviewed target genes and signaling pathways related to miR-802 may help researchers find a new therapeutic approach for the above cancers. Figure 2 summarizes the molecular effects of mir-02 in different types of cancers (Figure 2).

Table 1. miR-802 in different cancers.

Cancer type	MiR-802 target gene	Target gene ontology	Consequence	Experimental assays	Sample	Ref.
Osteosarcoma	Downregulate protein expression p27	Negative cell-cycle regulator	Osteosarcoma cell proliferation	TaqMan RT-PCR/ BrdU Assays/ Western blotting/ Luciferase reporter assay	Osteosarcoma tumor tissues and cell lines	[17]
Lung	menin	Tumor suppressor gene	Lung cancer cell proliferation	TaqMan RT-PCR/ BrdU Assays/ Western blotting/ Luciferase reporter assay	Lung tumor tissues and cell lines	[32]
	Ambient fine particulate matter (PM2.5)	higher lung cancer mortality and morbidity	Linked to down-regulation of miR-802 expression, dysregulation of the actin cytoskeleton, increased Rnd3 expression levels and consequently carcinogenesis	miRNA microarray analysis/ Proteomics analysis/ qRT-PCR/ F-Actin staining/ Histopathological analysis/ Immunohistochemistry staining/ Cell migration and cell invasion assays/ Colony formation analysis	Blood/ human and mouse lung tissue and cell lines	[33]
Breast	Downregulate expression of Forkhead box protein M1 (FoxM1)	An oncogene	Suppresses breast cancer proliferation	Quantitative polymerase chain reaction/ Cell proliferation assay/ Western blot analysis/ Luciferase reporter assay	Breast cancer cells, Nude mice	[35]
Prostate	flotillin-2	A flotillin family member that plays an important role in the pathogenesis and development of human malignancies	Suppression of EMT, migration, and invasion in prostate cancer cell lines	MTT assay, Flow cytometric analysis of apoptosis, quantitative polymerase chain reaction/ Western blot analysis/ Luciferase reporter assay	Prostate cancer cell lines, xenograft model	[37]
Liver	AKT/mTOR and Ras/MAPK cascades / c-Myc	Oncogene	Lower tumor burden in a c-Myc model	Microarray analysis/ Histology	c-Myc or AKT/Ras-induced liver cancer mouse models	[38]

Cancer type	MiR-802 target gene	Target gene ontology	Consequence	Experimental assays	Sample	Ref.
Hepatocellular Carcinoma	ZNF521	Tumor suppressor gene	Up regulation of miR-802 in tumor tissue suppress ZNF521	Quantitative RT-PCR/ MTT method/ Immunohistochemistry (IHC) / Cell proliferation/ luciferase reporter/ Western blot analyses	Hepatocellular carcinomas (HCC) tissues/ HCC cell lines/ Xenograft mouse model	[39]
Tongue squamous cell carcinoma	MAP2K4	Mitogen-activated protein kinase 4(kinase)	Tumor suppressor	Quantitative RT-PCR /invasion and migration assays/ luciferase reporter/ Western blot analyses/ CCK-8 assay	Tongue squamous cell carcinoma tissues and cell lines	[40]
Cervical cancer	Serine/arginine-rich splicing factor 9	Constitutive splicing	Tumor suppressor/ Cell cycle arrest at the G0/G1 phase and cell apoptosis	Quantitative real-time PCR/ Cell proliferation assay/ Colony formation assay/ Cell cycle analysis/ Western blot analysis/ Cell apoptosis assay/ Dual-luciferase reporter assay	Cervical cancer tissue/ Human cervical cancer cell lines	[41]
	basic transcription factor 3 (BTF3)	construct a stable complex with RNA polymerase IIB and is needed for initiation of transcription	Inhibition of EMT, invasion, and migration	Quantitative RT-PCR /invasion and migration assays/ luciferase reporter/ Western blot analyses	Cervical cancer tissue/ Human cervical cancer cell lines	[42]
Pancreatic cancer	Long non-coding RNA MIR155HG	Negative regulator of miR-802	Cancer progression	Proliferation and cell cycle analysis/ Quantitation of cell apoptosis/ Luciferase reporter assay/ Quantitative real-time PCR	Human pancreatic cancer tissue and cell lines	[44]
	Kras	oncogene	Cause acinar-to-ductal metaplasia (ADM)	Quantitative real-time PCR/ Western blot analyses	Human pancreatic cancer tissue/mice models	[45]
Ovarian cancer	YWHAZ	Member of 14-3-3 gene family and have a role in tumor migration, regulation of signal transduction, and apoptosis inhibition	Causes migration and proliferation of epithelial ovarian cancer cells	Quantitative real-time PCR/ Cell proliferation assay/ Colony formation test/ Migration and invasion assay/ Apoptosis analysis/ Dual-luciferase reporter gene assay/ Western blot analyses	Ovarian cancer tissues and cell lines	[46]
Colorectal cancer	Rasassociated nucleus (RAN)	oncogene	inhibits migration and proliferation of colorectal cancer cells	Quantitative real-time PCR/ Cell proliferation assay/ Migration and invasion assay/ Dual-luciferase reporter gene assay/ bioinformatics studies	colorectal cancer tissues and cell lines/ mouse model	[47,48]

4. Pathophysiological Role of miR-802 in Down Syndrome

The miR-802 gene is located on human chromosome 21, in addition to four other important miRs, including miR-99a, let-7c, miR-125b-2, and miR-155. All of these miRs are

overexpressed in the brain and heart of down syndrome (DS) individuals in comparison with the control group, which is resulted from trisomy 21 gene dosage, and are involved in disease symptoms [49].

Other studies have confirmed the overexpression of miR-802 in DS individuals, besides identifying some of its targets in human or mice brain specimens [50,51]. It has also been reported that methyl-CpG-binding protein (MeCP2) is the target of miR-802, and its translation decreases following overexpression of miR-802. Downregulation of MeCP2 resulted in deregulation in CREB1/Creb1 and MEF2C/Mef2c genes which are under the control of MeCP2 and have a function in neuronal development [52-54]. Although there is a report that has not shown any difference in the expression of miR-802 in the hippocampus between down syndrome model mouse Ts65Dn (with an extra copy of a segment of genes on chromosome 16) and euploid control mice, Keck-Wherley *et al.* reported miR-802 overexpression in hippocampus and blood of Ts65Dn [55]. In this study, functional analysis on target genes of 12 overexpressed miRNA in the hippocampus of Ts65Dn, including mir-802, was performed, and nervous system development was among physiological functions [55].

Malfunction of neurogenesis has been investigated in a study in which induced pluripotent stem (iPS) cells were produced from trisomy 21 amniotic fluid cells (T21 AF-iPS cells) by co-expressing Yamanaka factors, and in the next step, iPS cells were differentiated into neuronal progenitor cells (NPCs). The expression levels of miR-802 and miR-155 and the level of amyloid precursor protein were higher in T21 AF-iPS cells compared to NPCs generated from normal AF-iPS cells. Still, the level of MeCP2 protein and numbers of generated neurons was lower in T21 AF-iPS cells, and these cells showed developmental impairment during neurogenesis [56].

Furthermore, in a genome-wide microRNA expression study on the fetal cord blood mononuclear cells (CBMCs) of DS and normal fetuses, the expression levels of miR-802 were upregulated, which was confirmed by qPCR assay [57].

In another genome-wide study, the effect of miR-802 upregulation on the Ts65Dn mouse model brain transcriptome was investigated. Following the injection of miR-802 lentiviral sponges in the hippocampus of Ts65Dn, miR-802 expression was decreased, resulting in an elevation in the expression of its targets such as SH2 (Src homology 2)-containing inositol phosphatase-1 (Ship1), methyl-CpG-binding protein 2 genes (Mecp2) and Forkhead box protein M1 (FoxM1). Transcriptomic data demonstrated significant associations in a subset of genes (Nova1, Rufy2, Sumo3, Thoc1, and Nav1) with miRNA dosage [58].

5. Pathophysiological Role of miR-802 in Immune System-Mediated Conditions

There are some reports of miR-802 role in immune system-mediated impairment, such as inflammatory responses, cell proliferation, T-cell exhaustion, and fibrosis. In a study, it has been demonstrated that the inflammatory signaling pathway of NF- κ B in Cholesteatoma (middle ear abnormal and destructive skin growth) induces miR-802 overexpression through binding of P65 to the miR-802 promoter, which is verified by chromatin immunoprecipitation assays. Subsequently, overexpressed miR-802 increases keratinocyte cell cycle progression and cell proliferation, which play pivotal roles in disease development [59]. The possible role of miR-802 in obesity-associated nephropathy has also been demonstrated in another study. Renal structural disorders, dysfunction, fibrosis, infiltrated macrophages, and inflammatory response in the kidney of high-fat diet mouse decreased via renal miR-802 specific silencing.

In this regard, inhibiting the NF- κ B-repressing factor (NRF) and downregulating its expression has been reported as a possible mechanism of action of miR-802 [60].

Another group of researchers studied oral lichen planus (OLP), a condition characterized by epithelial layer dysfunction and T-cell infiltration into the lamina propria. They suggested that vitamin D suppresses miR-802 expression by targeting the NF- κ B pathway by disrupting the NF- κ B p65 binding site to the miR-802 promoter. In this way, vitamin D can suppress miR-802 functions by targeting B-cell lymphoma 2 mRNA and inducing oral keratinocytes apoptosis in OLP [61,62].

In hepatocellular carcinoma patients, it is reported that upregulation of miR-802 induced T-cell exhaustion through declining regulating DNA damage response 1 (REDD1) and interferon- γ (IFN- γ) and increased the programmed cell death protein 1 (PD-1) expression [63].

The molecular effects of miR-802 in inflammatory bowel disease (IBD) have been studied. Upregulation of miR-802 in inflamed mucosa, CD4+ T cells, and PBMC cells of IBD indicate the role of this miRNA in the inflammatory process of IBD. The molecular mechanism of miR-802 is suggested to be by downregulation of SOCS5. In addition, secretion of TNF- α and differentiation of Th17 are other effects that have been imputed to miR-802 overexpression in IBD [64].

6. Other Pathophysiological Role of miR-802

Apart from the above-mentioned roles, miR-802 also has other physiological functions in the kidney, intestine, and liver. Overexpression of miR-802 has been reported in the kidney of high potassium (K⁺) fed animals through microarray assay by Lin *et al.*, which resulted in caveolin-1 suppression. Caveolin-1 interacted with renal outer medullary potassium (ROMK) channels and inhibited its activity. So, miR-802 mediates overexpression of ROMK channels on the surface of the distal nephron under the high-potassium diet [15]. In addition, overexpression of miR-802 in exosomes of patients with chronic kidney disease (CKD) and animal models of human CKD and Alport syndrome were verified [65,66].

In the intestine, loss-of-function of miR-802 results in overexpression of ATR(1) as a G protein-coupled receptor subtype and subsequently affect angiotensin II function in modulating intestinal electrolyte and fluid transport [67]. miR-802 also regulates enterocyte differentiation and paneth cell function in the mouse small intestine [68]. The other physiological function known for miR-802 is providing sex-differential gene expression under the regulation of growth hormone (GH) in the liver of female mouse. Studies in pre-pubertal and young adult mice demonstrated that sex-specific secretory patterns of pituitary GH control the female-biased miR-802 acquire sex specificity at puberty. Besides, findings from an *in vivo* study through inhibitory locked nucleic acid sequences have shown that miR-802 is responsible for male-biased and female-biased mRNAs suppression and induction, respectively [69].

7. Conclusions

MicroRNAs have vast regulatory and tuning functions in different cellular and molecular processes and networks that. Any dysregulation of them results in different pathophysiological malfunctions [70,71]. Similarly, it is demonstrated that miR-802 has diverse, important, and emerging pathological and physiological roles, especially in metabolism, cancer, neuropathology, and Down syndrome. As mentioned, glucose metabolism is one of the important areas that miR-802 plays a role in [16]. In this regard, an interesting

research era in which the function of miR-802 can be further investigated is cancer metabolism pathways. There are some reports on reprogramming cancer metabolism for cancer therapy, and because of the validated roles of miR-802 both in cancer and glucose metabolism, it seems miR-802 would be an interesting target to explore its role in this field [72,73]. Developing high throughput techniques such as microarray, NGS, and proteomic, besides knock out and gene silencing ones, has made the miR-802 identification, quantification, and function determination more precise and practical [16,22,57,69]. On the other hand, bioinformatics analysis for understanding the basis of the disease is getting more and more applicable [74,75].

Therefore, we suggest more bioinformatics study on clinical data of miR-802 is needed to elucidate this microRNA's unknown mechanisms of action in cancer, immune system-mediated conditions, metabolism, and so forth. Taking together, it seems identification of miR-802 targets and mechanisms of their action can provide a better understanding of molecular bases and a novel therapeutic approach for the treatment of disease phenotype. Although a great effort was made to decipher the role of miR-802 in the molecular basis of diseases, more comprehensive analysis and clinical studies are urgently required to determine its pathological functions and therapeutic capacity.

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Conflicts of Interest

The authors declare no conflict of interest.

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