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Mini Review

A Review of the Biological Roles of MiR-4800; A Novel Tumor Biomarker with Therapeutic Potential

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Abstract

MicroRNAs (miRNAs) are known as a group of short noncoding ribonucleic acids (ncRNAs). Mainly, they can manage gene expression at the posttranscriptional level in the essential biological and physiological functions. Significantly, more than 50% of the discovered miRNAs genes are placed in cancer-related genomic regions, which can act as oncomiR or oncosuppressor. In this regard, growing evidence recently demonstrated the deregulation of miR-4800 in human cancers and non-cancerous diseases. However, little information is available on the biological roles of miR-4800 in cancer initiation, development, and progression. Here, we reviewed the targeting sites and biogenesis functions of the miR-4800 family in physiological and pathological processes like human cancers, particularly with a particular focusing on the validated specific targets.

Introduction

MicroRNAs (miRNAs), which structurally include 18-25 nucleotides in length, are known as a group of short noncoding ribonucleic acids (ncRNAs). Mainly, they can manage gene expression at the posttranscriptional level through the specific targets in the essential biological and physiological functions, such as cell growth and proliferation, cell motility, differentiation, and organ development.[1,2] Besides, it was suggested that these small RNAs could contribute to the initiation, progression, and development of disease and cancer conditions.[2,3] In this regard, it has been previously proposed that more than 50% of the discovered miRNAs genes are placed in cancer-related genomic regions, which can act as oncomiR or oncosuppressor and contribute to the development of solid and hematological malignancies.[4] They strongly modulate angiogenesis, migration, and metastatic processes. Among these tiny molecules, several studies have been recently reported dysregulation of miR-4800 in non-cancerous diseases and human cancers. Briefly, Deregulation of miR-4800 (including miR-4800-3p and miR-4800-5p) was reported in various cancers such as breast cancer,[5-7] cervical cancer,[8] colorectal cancer,[9,10] esophageal squamous cell carcinoma (ESCC),[11] gastric cancer,[12] glioma,[13] liver carcinoma,[14] and pancreatic cancer.[15] Indeed, the upregulation of miR-4800 was investigated in the serum or tissue samples of the patients with these cancers. Recently, miR-4800 has been presented as a circulating miRNAs for diagnosis of oral squamous cell carcinoma.[16] However, little information is available on the biological roles of miR-4800 in cancer initiation, development, and progression.

MiR-4800 Family

This gene with a 4p16.3 chromosomal location has one transcript. Based on miRBase,[17] this precursor RNA sequence (URS000075B063-9606) is 80 nucleotides long, which is found in Homo sapiens (hsa). Indeed, the family of miR-4800 includes has-miR-4800-3p and has- miR-4800-5p, which consists of 21 and 19 nucleotides in mature sequences,[18] respectively (Figure 1). These are short non-coding RNAs that are highly conserved during evolution in the mature form. This RNA has nine ortholog/paralog sequences investigated by Ensembl Compara (Figure 2, tree) in *Cercocebus atys* (Sooty mangabey), *Gorilla gorilla gorilla* (Western Lowland Gorilla), *Macaca fascicularis* (Crab-eating macaque), *Macaca mulatta* (rhesus monkey), *Macaca nemestrina* (Pig-tailed macaque), *Mandrillus leucophaeus* (Drill), and *Pan paniscus* (bonobo).

Validated Targets of miR-4800 and Related Biological Functions

MicroRNAs regulate gene expression by targeting messenger RNAs. According to the Next Generation Sequencing (NGS), some validated targets of miR-4800-5p to gather with related biological roles have been identified in miRBase. But, little information is available on the miR-

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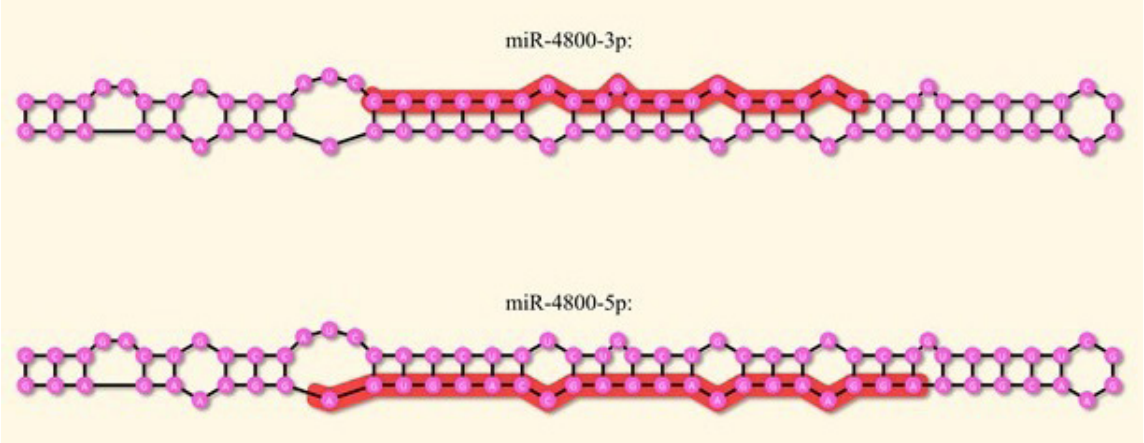

Figure 1. Mature sequences of miR-4800-3p and miR-4800-5p.

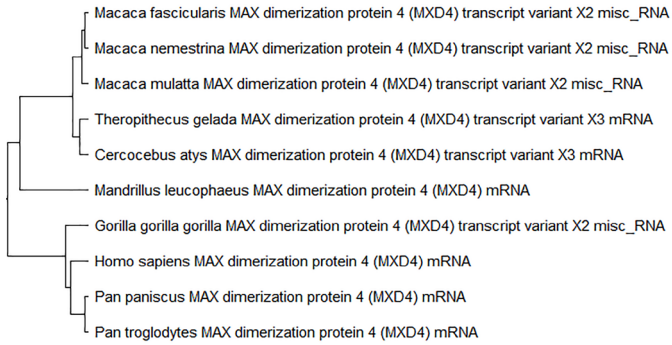

Figure 2. Ortholog/paralog sequences of miR-4800 identified by Ensembl Compara.

4800-3p targets and roles in biological processes (Figure 3). Although, some databases suggest a large number of predicted targets for the miR-4800 family. In this connection, Target Scan Human[19,20] reports 426 transcripts with sites, consisting of a total of 441 sites for miR-4800-3p, and 2234 transcripts with sites, comprising a total of 2627 sites for miR-4800-5p. Moreover, miRDB[17] reports 14 and 144 predicted targets for hsa-miR-4800-3p and hsa-miR-4800-5p, respectively. Briefly, we explain here about some miR-4800 targets and related biological functions.[21]

BUB3 (BUB3 mitotic checkpoint protein). It locates on Chr10: NC-000010.11, which is known as a WD40 protein affiliated to the spindle mitotic checkpoint complex. It modulates the chromosome attachment to mitotic (or meiotic) fuse and inhibits premature chromosome segregation. Conversions in BUB3 have been connected with chromosomal instability and aneuploidy. However, their role in cancer development is poorly determined.[22]

LRWD1 (leucine-rich repeat and WD repeat-containing protein 1). It locates on Chr7: NC-000007.14, which plays an important role in the cell cycle, such as G1/S phase transition and DNA methylation.

TXNIP (Thioredoxin interacting protein). It locates on Chr1: NC-000001.11 and encodes a thioredoxin-binding protein, which acts as a modulator of cellular metabolism and endoplasmic reticulum stress. Indeed, this protein is one of the principal regulators of cellular redox signaling, which inhibits the accumulation of reactive oxygen species and protects cells from oxidative stress. Importantly, it is proposed that it may also function as a tumor suppressor.[23]

IGF1R (Insulin-like growth factor 1 receptor). It locates on Chr15: NC-000015.10 and binds insulin-like growth factor, and has tyrosine kinase activity, which plays an essential role in transformation events. Besides, it is significantly overexpressed in malignant tumors with an anti-apoptotic activity that enhances cell survival.[24]

ECSIT (ECSIT signaling integrator). It locates on Chr19: NC-000019.10, which contributes to the proteolytic activation of MAP3K1 and normal embryonic development.[25] Besides, further studies proposed other functions such as regulation of mitochondrial reactive oxygen species production,[26,27] phagocytosis of bacteria by macrophages[28] and intracellular bacterial clearance.[26]

PEX10 (Peroxisomal biogenesis factor 10). It locates on Chr1: NC-000001.11 and encodes a protein involved in the import of peroxisomal matrix proteins, which localizes to the peroxisomal membrane. Mutations and alterations in this gene lead to peroxisomal biogenesis disorders.

GATA6 (GATA binding protein 6). It locates on Chr18: NC-000018.10, which is one of the members of a small family of zinc finger transcription factors that plays a critical role in modulating cellular differentiation and organogenesis. It is occasionally expressed during early embryogenesis and subsequently confines in endo- and mesodermally derived cells during later embryogenesis. Mutations in this gene are related to several congenital

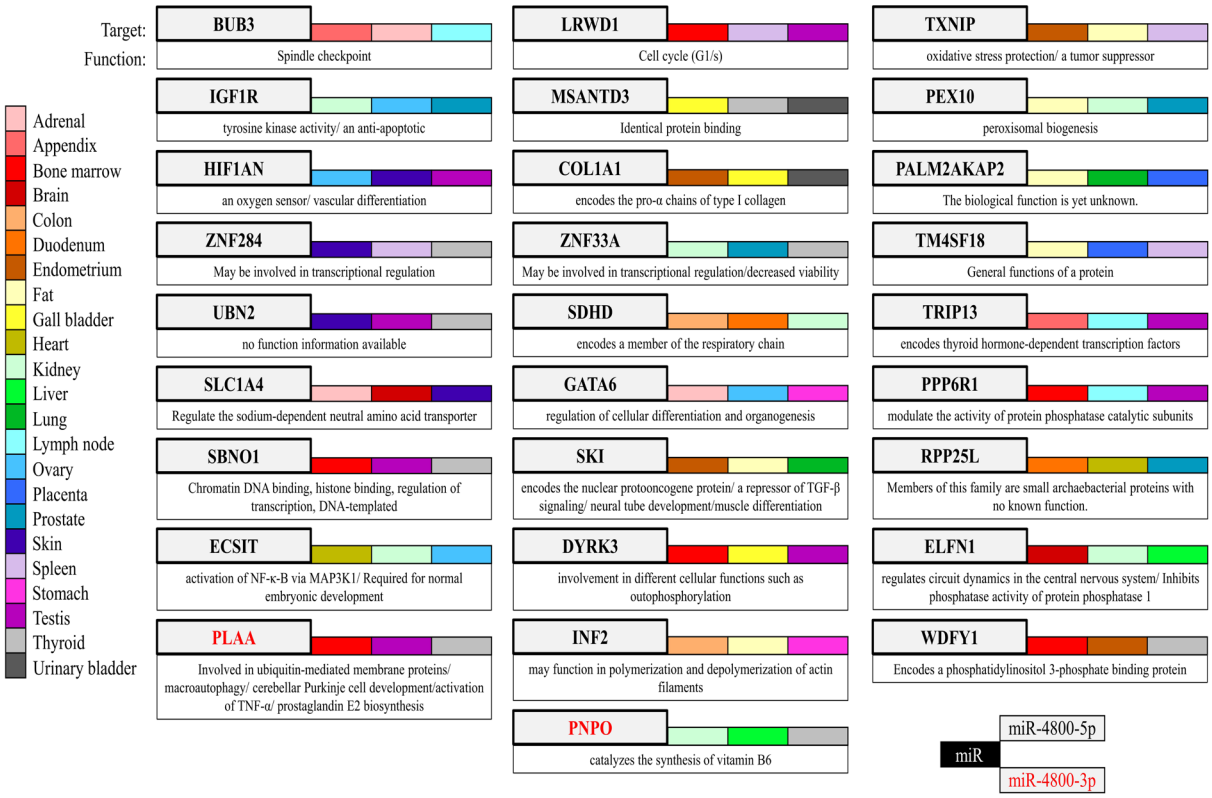

Figure 3. miR-4800 targets and related biological functions.

disorders, cardiovascular diseases,[29] gastric cancer,[30] and ovarian cancer.[31]

SLC1A4 (Solute carrier family 1 member 4). It locates on Chr2: NC-000002.12 and encodes a protein, which is a sodium-dependent neutral amino acid transporter for serine, cysteine, alanine, and threonine. Alterations in this gene can result in developmental delay, microcephaly, and intellectual disability.[32]

SKI (SKI proto-oncogene). It locates on Chr1: NC-000001.11 and encodes a nuclear proto-oncogene protein homolog of avian sarcoma viral oncogene. It inhibits TGF-beta signaling and manages muscle differentiation and neural tube development.[33]

HIF1AN (Hypoxia-inducible factor 1 subunit alpha inhibitor). It locates on Chr10: NC-000010.11. Briefly, it acts as an oxygen sensor and, the hydroxylation inhibits the interaction of HIF-1 with transcriptional co-activators under normoxic conditions. It also accelerates myogenic and vascular differentiation.[34]

ELFN1 (Extracellular leucine-rich repeat and fibronectin type III domain containing 1). It locates on Chr7: NC-000007.14. It was shown to contributes to circuit dynamics in the central nervous system and represses phosphatase activity of protein phosphatase 1 complex.[35]

COL1A1 (Collagen type I alpha 1 chain). It locates on Chr17: NC-000017.11 and encodes the pro-alpha1 chains of type I collagen, which is found in most connective tissues. Mutations in this gene are related to Ehlers-Danlos syndrome, Caffey Disease, osteogenesis imperfecta, and idiopathic osteoporosis.[36]

ZNF33A (Zinc Finger Protein 33A). It locates on Chr10: NC-000010.11, and it may be contributed to transcriptional regulation. A cytoplasmic positivity with various grades of expression (high/medium/moderate/low) was identified in several human malignancies such as breast, prostate, cervical, urothelial, thyroid, gliomas, endometrial, and stomach cancers.[37]

SDHD (Succinate dehydrogenase complex subunit D). It locates on Chr11: NC-000011.10 and encodes one of two integral membrane proteins anchoring the complex II of the respiratory chain to the matrix side of the mitochondrial inner membrane, which is responsible for the succinate oxidation. It was determined that alterations of this gene are related to the development of some tumors, such as paraganglioma[38] and carotid body tumor.[39]

DYRK3 (Dual specificity tyrosine phosphorylation regulated kinase 3). It locates on Chr1: NC-000001.11 and encodes a protein kinase family that their involvement in various cellular functions. For example, it seems that they catalyze autophosphorylation of serine/threonine and tyrosine residues.[40]

TRIP13 (Thyroid hormone receptor interactor 13). It locates on Chr5: NC-000005.10 and is determined as hormone-dependent transcription factors, and the encoded proteins interact with thyroid hormone receptors. It was shown that this gene might involve in early-stage non-small cell lung cancer. Besides, it was recently determined in bladder cancer,[41] hepatocellular carcinoma,[42] and Wilms tumor.[43]

INF2 (Inverted formin 2). It locates on Chr14: NC-000014.9 and encodes a member of the formin family of proteins contributing to polymerization and depolymerization of actin filaments. Considerably, it seems that mutations in this gene are related to focal segmental glomerulosclerosis.[44]

PNPO (Pyridoxamine 5'-phosphate oxidase). It locates on Chr17: NC-000017.11 and encodes an enzyme that catalyzes the terminal, rate-limiting step in the synthesis of pyridoxal 5'-phosphate, also identified as vitamin B6. Mutations in this gene lead to neonatal encephalopathy.[45] Moreover, it was associated with human breast invasive ductal carcinoma.[46]

PLAA (phospholipase A2 activating protein). It locates on Chr9: NC-000009.12 and encoded proteins involved in various cellular functions, such as ubiquitin-mediated membrane proteins, synaptic vesicle recycling, macroautophagy, cerebellar Purkinje cell development, and prostaglandin E2 biosynthesis, and a novel form of leukoencephalopathy.[47,48]

MiR-4800 and Non-Cancerous Diseases

The expression level of miR-4800-5p was upregulated (with a 2.34-3.69 fold change) in the fresh plasma samples of the patients with chronic hepatitis B virus infection during the progression of hepatic fibrosis.[49] Upregulation of miR-4800-5p was found in plasma samples of the children with acute Kawasaki disease (a systemic vasculitis syndrome) by microarray and q-RT-PCR analyses.[50] The expression level of miR-4800-5p was upregulated in the plasma samples of the patients with sepsis secondary to pneumonia by fluorescence q-RT-PCR.[51] A significant upregulation of miR-4800-3p was detected in enterovirus 71-infected cells with 28.83 fold change.[52] Downregulated expression of miR-4800-5p was determined in keloids (a pathological scar) with 0.004 fold change.[53] Also, it was recently proposed that miR-4800 is the most downregulated miRNA in human endothelial cells after exposure to two realistic doses of fine particulate matter ($PM_{2.5}$) with aerodynamic diameters and showed the possible gene targets of deregulated miRNA through microarray profiling and computational technology.[54]

MiR-4800 and Human Cancers

Emerging evidence proposed that miR-4800 is an intragenic miRNA involved in carcinogenesis.[55] Besides, it was reported that miRNA-4800 acts as a regulator of tumor suppressor expression. For example, the expression level of the BAI1 gene is regulated by ex-miR-4800-5p, which is bound to the CDS, and ex-miR-4800-3p, which bound with the 3′UTR.[56] Dysregulation of miR-4800 (including miR-4800-3p and miR-4800-5p) that is recovered recently was reported in various cancers (Figure 4).

MiR-4800 was presented as one of the up-regulated miRNAs in triple-negative breast cancer (TNBC). TNBC is identified by the lack of expression of the progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER-2). TNBC, approximately 15-20% of total breast cancer cases, presents a more aggressive manner associated with a more unsatisfactory clinical outcome than other breast cancer subtypes.[5] Also, another previous study reported miR-4800 as one of the up-regulated miRNAs of BT474 cells with HER-2 gene intervention. Receptor tyrosine-

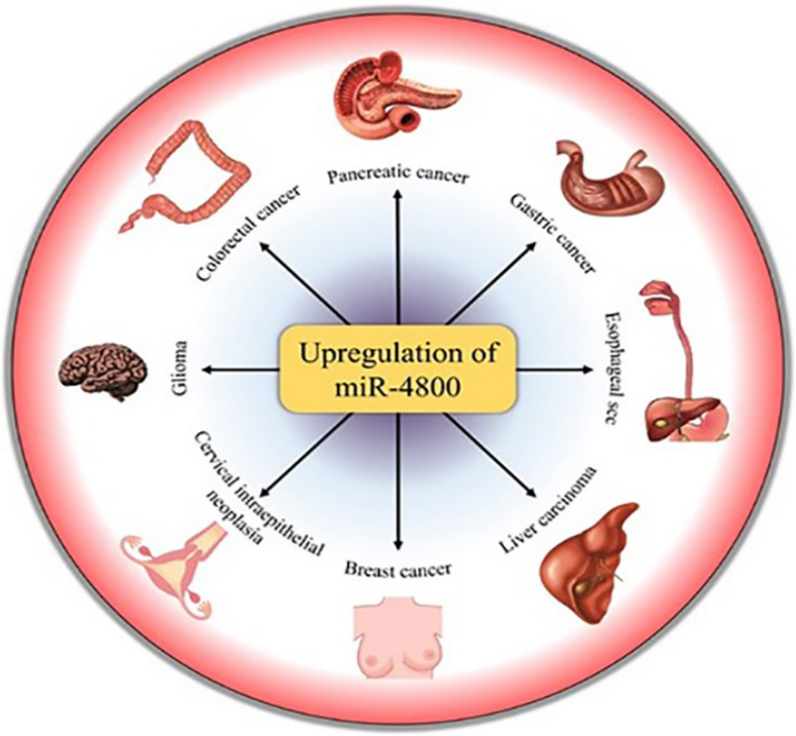

Figure 4. Dysregulation of miR-4800 that is recovered recently was reported in various cancers.

protein kinase ERBB2 (HER-2) represents a key role in the development and progression of aggressive subtypes of breast cancer, which was suggested as an important target of therapy for breast cancer.[6] Besides, miR-4800 has been found as one of the up-regulated miRNAs in the fulvestrant-resistant (MCF7-F) cell line. Fulvestrant is one of the major endocrine drugs that targeting estrogen receptor-α to treat ER-α-positive breast cancer patients. Importantly. It is administrated as second-line therapy for breast cancer patients with metastatic behavior, which can be valuable in guiding drug selection.[7]

Upregulation of miR-4800-3p was reported in the cervical intraepithelial malignancies in formalin-fixed, paraffin-embedded samples by microarray and q-RT-PCR methods.[8] Also, Mir-4800 was one of the upregulated miRNAs in esophageal squamous cell carcinoma (ESCC) tissues with 2.2 fold change by microarray analysis.[11]

It was recently determined that miR-4800-5p overexpressed in the early stage of gastric cancer patients from Saudi Arabia population with 1.51 fold change.[12] Meanwhile, overexpression of miR-4800-5p was shown in colorectal cancer tissues with 0.41 fold change.[9] Besides, upregulated miR-4800-5p was found in the serum samples of colorectal cancer patients with a 3.01 fold change. Interestingly, the expression of miR-4800-3p was reduced with 0.41 fold change in the same samples.[10] Recently, it was indicated that miR-4800 is one of 20 miRNAs remarkably inversely modulate IQGAP3 (IQ-domain GTPase-activating proteins) in hepatocellular carcinoma (by bioinformatics analysis), which acts as an oncogene and regulate cellular physiology, including cell adhesion, cell migration, extracellular signals, and cytokinesis.[14] Very recently, miR-4800 has been indicated as one of the prognostic factors affecting the survival of patients with hepatocellular carcinoma.[57,58] It was reported that there was no significant difference in the expression level of miR-4800-3p in the serum exosomes of pancreatic cancer patients compared with healthy donors.[15]

A previous study proposed that miR-4800-3p (with 0.85 fold change) is one of the upregulated miRNAs induced by xanthohumol (has potential for cancer therapy) cytotoxicity in glioblastoma U87 MG cells.[13]

MiR-4800 as a Potential Biomarker

One of the notable applications of miRNAs is the early detection of various diseases, mainly those which considered cancer detection. Of note, they can be easily used and diagnosed in fixed tissues samples, blood circulation, and human body fluids.[59] In this regard, upregulation of miR-4800-5p was revealed in plasma samples of the patients with chronic hepatitis B virus infection and the children with acute Kawasaki disease.[49,50] Overexpression of miR-4800-5p was reported in triple-negative breast cancer, colorectal cancer, esophageal squamous cell carcinoma, and gastric cancer tissues.[5,9,11,12] Moreover, upregulation of miR-4800-3p was indicated in the cervical malignancies in formalin-fixed samples.[8] Notably, the expression level of miR-4800-3p reduced in the serum samples of colorectal cancer patients.[10] Besides, miR-4800 has been determined as one of the prognostic factors impacting the survival of patients with hepatocellular carcinoma.[57,58]

Conclusion

Taken to gather, the members of the miR-4800 family, including miR-4800-5p and miR-4800-3p, play a considerable role in the crucial biological mechanisms, pathological processes of human diseases, and initiation and progression of various cancers by directly specific targets and molecular pathways. However, few experimental studies have been performed on the exact functions and validated targets of miR-4800. Furthermore, it is essential that further studies must investigate the role of this miRNA in the various cancer processes, such as cell proliferation, apoptosis, cell motility and migration, angiogenesis, and metastasis. Moreover, it could be paid attention as a specific potential diagnostic, predictive, and prognostic tool in various human diseases.

Author Contributions

MKh reviewed the state of the art on the topic and wrote the article; RM, AB, FJA, and FK focused on the basic aspect of the review and wrote the article; BB guided the present scientific team, wrote and revised the article. All authors study and approved the final manuscript.

Conflict of Interest

The authors report no conflicts of interest.

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