miR-1908: a microRNA with diverse functions in cancers and non-malignant conditions

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Abstract

MicroRNAs (miRNAs) are small-sized transcripts with about 22 nucleotide length. They have been shown to influence almost every aspect of cellular functions through regulation of expression of target genes. miR-1908 is a miRNA with diverse roles in human disorders. This miRNA is encoded by MIR1908 gene on chr11:61,815,161–61,815,240, minus strand. Expression assays have confirmed dysregulation of miR-1908 in cancer-derived cell lines in addition to biological samples obtained from patients affected with cancer. In most assessed cell lines, miR-1908 has an oncogenic role. However, this miRNA has been shown to act as a tumor suppressor in chordoma, lung cancer and ovarian cancer. In addition, several lines of evidence have shown involvement of this miRNA in the pathoetiology of bipolar disorder, myocardial infarction, obesity, renal fibrosis, rheumatoid arthritis and scar formation. In the current review, we elucidate the results of diverse studies which evaluated participation of miR-1908 in these conditions.

Keywords: miR-1908, Cancer, Bipolar disorder

Introduction

MicroRNAs (miRNAs) are a group of regulatory non-coding RNAs with sizes about 22 nucleotides [1]. In multicellular organisms, miRNAs affect both the stability and translation of mRNAs, thus participating in modulation of gene expression at post-transcriptional level. RNA polymerase II-mediated transcription of miRNAs leads to production of capped and polyadenylated primary transcripts, which are then, cleaved by a specific type of ribonuclease III enzymes. This enzymatic process results in production of stem-loop structures with approximate size of 70 nucleotides. These so-called precursor miRNAs are subjected to another round of cleavage by the cytoplasmic Dicer ribonuclease. The mature miRNA produced by these two rounds of processing is assimilated into a RNA-induced silencing complex (RISC). RISC identifies target mRNAs via a base pairing process resulting in suppression of mRNA translation or its destabilization [2]. miRNAs contribute in diverse biological processes for example cell proliferation, differentiation and apoptosis, thus contributing in the pathoetiology of diverse disorders [3, 4].

miR-1908 is encoded by MIR1908 gene on chr11:61,815,161–61,815,240, minus strand. The stem loop sequence of this miRNA is as follows: CGGGAAA UGCCGCGCGGGAACGGCAGUGGGCGUA UUGUGUGGCGACCGCCGCCCGCCGUCGGCC CCGGC CGGGCC (https://www.mirbase.org/cgi-bin/mirna_entry.pl?acc=MI0008329).

This miRNA contains some single nucleotide polymorphisms (SNPs). Genome wide association studies (GWAS) and evaluation of human regulatory elements (enhancers and promoters) have indicated association between these SNPs and red blood cell distribution width, serum metabolite levels, neuroimaging measurement, brain volume measurement, asthma, bipolar...
disorder, and response to carboplatin (https://www.genecards.org/cgi-bin/carddisp.pl?gene=MIR1908). Thus, this miRNA is regarded as a candidate gene for several human phenotypes and disorders. Expression assays have also confirmed abnormal expression levels of miR-1908 in cancer-derived cell lines as well as biological samples obtained from patients affected with cancer. In addition, several lines of evidence have shown involvement of this miRNA in the pathoetiology of bipolar disorder, myocardial infarction, obesity, renal fibrosis, rheumatoid arthritis and scar formation. In the current review, we elucidate the results of diverse studies which evaluated participation of miR-1908 in these conditions. The reason of selection of this miRNA was its newly identified roles in diverse cancers, particularly its opposite roles in different contexts.

The impact of miR-1908 in the carcinogenesis based on cell line studies
Experiments in two breast cancer cells have indicated the role of miR-1908-3p in enhancement of cells proliferation, migration and invasion [5]. Further evaluations in these context have potentiated ID4, LTBP4, GPM6B, RGMA, EFCAB1, ALX4, OSR1 and PPARA as targets of this miRNA [5].

In cervical cancer cell lines, expression of miR-1908 has been found to be upregulated. Over-expression of miR-1908 has augmented growth and invasion of cervical carcinoma cells. Consistently, miR-1908 silencing has led to opposite effect. In silico and functional studies have validated interaction between miR-1908 and HDAC10. Besides, ectopic expression of HDAC10 in cervical cancer cells could reverse the effect of miR-1908 to some extent. Taken together, miR-1908 increases aggressive behavior of cervical cancer cells through targeting HDAC10 [6].

Up-regulation of miR-1908 in glioblastoma cells has enhanced anchorage-independent growth. This miRNA could suppress PTEN expression through binding with its 3’-UTR. Thus, miR-1908 has an oncogenic role in glioblastoma through inhibition of PTEN pathway [7]. Another study in glioma has shown that miR-1908 has a role in enhancement of proliferation and invasion, as well as suppression of apoptosis through regulation of SPRY4/RAF1 axis. In silico analyses has indicated involvement of miR-1908 in the regulation of pathways related with cell proliferation, invasion and apoptosis. Up-regulation of miR-1908 has induced anti-apoptotic effects in glioma cells via reducing expression levels of Bax. SPRY4 as one of validated miR-1908 targets has interactions with the pro-oncogene RAF1. Up-regulation of miR-1908 has led to down-regulation of SPRY4 expression and up-regulation of RAF1 [8].
shows the molecular axes mediating the oncogenic roles of miR-1908 in a number of cancers.

Contrary to the bulk of evidence in the above-mentioned types of cancers, miR-1908 has been shown to induce tumor suppressor impacts in ovarian cancer and lung cancer (Fig. 2). An in vitro study in non-small cell lung cancer has indicated down-regulation of miR-1908. miR-1908 mimics could reduce proliferation of these cells. Furthermore, RP-p53 pathway has been shown to be activated by miR-1908 mimics. The suppressor of the RP-p53, AKT1S1 has been found to be targeted by miR-1908 [9].

Table 1 summarizes the results of in vitro studies on the role of miR-1908 in the carcinogenesis.

**Function of miR-1908 in non-malignant disorders based on studies in cell lines**

A single study in the context of bipolar disorder has stated that a number of validated targets of miR-1908-5p, namely DLGAP4, GRIN1, STX1A, CLSTN1 and GRM4 are involved in the regulation of glutamatergic synapses in neurons. Besides, in silico assessments have also confirmed inverse correlation between expression of miR-1908-5p and these synaptic targets in many regions of human brain. Expression levels of miR-1908-5p in normal human neural progenitor cells have been surged following chronic treatment with valproate. However, treatment of these cells with lithium has not affected expression of this miRNA. Most notably, valproate has reduced expression of this miRNA in neural progenitor cells originated from fibroblasts of a patient with bipolar disorder. Cumulatively, miR-1908-5p has been suggested to contribute in the pathogenesis of bipolar disorder [15].

Another study has indicated that over-expression of miR-1908 can improve cardiac function, decrease fibrosis of myocardial cells and decrease TGF-β1 and Smad2/3 levels. TGF-β1 has been shown to be targeted by miR-1908. In fact, miR-1908 inhibits expression of Smad2/3 via TGF-β1 [16].

Levels of miR-1908 have been shown to be elevated in the course of adipogenesis of human multipotent adipose-derived stem cells. Up-regulation of miR-1908 in these cells could inhibit adipogenic differentiation and enhanced proliferation of cells, demonstrating the effect of this miRNA in the differentiation and metabolism of adipocytes and pathogenesis of obesity [17]. Table 2 shows function of miR-1908 in non-malignant disorders based on studies in cell lines.

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![Fig. 2 Tumor suppressor role of miR-1908](image-url)
Animal studies on the role of miR-1908 in cancers and non-malignant conditions

Few animal studies have assessed function of miR-1908 in animal models. Two studies have confirmed the oncogenic roles of miR-1908 in glioblastoma [7] and osteosarcoma [12] (Table 3).

Moreover, contribution of miR-1908 in the pathogenesis of myocardial infarction, renal fibrosis and scar formation has been verified in animal models (Table 4).

Tumor suppressor versus oncogenic roles of miR-1908 based on studies in clinical samples

Expression of miR-1908-3p has been reported to be elevated in breast cancer tissues and sera of these patients compared with corresponding controls. Besides, its expression has been higher in tissue samples of young patients and HER2-positive samples compared with samples obtained from older patients and HER2-negative tumors, respectively. Similarly, serum level of miR-1908-3p has been higher in younger patients compared with elder ones. Most notably, higher levels of miR-1908-3p target genes have been correlated with better clinical outcomes in this type of cancer [5].

In cervical cancer samples, the expression of miR-1908 has been inversely correlated with transcript levels of HDAC10. Notably, over-expression of HDAC10 has been associated with better prognosis of cervical cancer [6].

In glioblastoma, miR-1908 expression has been significantly higher in the patients with high risk of tumor recurrence compared to those with lower risk of recurrence. Moreover, over-expression of miR-1908 has been correlated with poor survival of patients. Taken together, miR-1908 has been regarded as a putative biomarker for estimation of risk of recurrence in patients with glioblastoma [7]. Another study has shown down-regulation of SPRY4 as one of validated targets of miR-1908 in glioma samples. Markedly, down-regulation of SPRY4 has been correlated with short survival time in these patients [8].

Table 1  Function of miR-1908 in cancers based on studies in cell lines (∆: knock-down or deletion)

| Tumor type          | Interactions                      | Cell lines | Function                                                                 | Exact role       | References |
|---------------------|-----------------------------------|------------|--------------------------------------------------------------------------|------------------|------------|
| Breast cancer       | ID4, LTBP4, GPM6B, RGMA, EFCAB1, ALX4, OSR1 and PPARA | MCF-10A, MCF-7, MDA-MB-231 | ↑↑ miR-1908-3p: ↑ proliferation, migration and invasion | Oncogenic        | [5]        |
| Cervical cancer     | HDAC10                             | Ca-Ski, SiHa, C-4-I and Endl/ E6E7 | ↑↑ miR-1908: ↑ cell growth and invasion | Oncogenic        | [6]        |
| Glioblastoma        | PTEN, AKT/FOXO3a and AKT/mTOR pathways | A127, SW1783, U87, U373, LN-229, SW1088, HS683, HFU251, SNB19, 9T8G, 1228 and 802 | Δ miR-1908: ↓ proliferation, viability, invasion and sphere formation | Oncogenic        | [7]        |
| Glioma              | SPRY4/RAF1 axis                    | U251       | ↑↑ miR-1908: ↑ proliferation, invasion and ↓ apoptosis                  | Oncogenic        | [8]        |
| Nasopharyngeal cancer | –                                 | P109CD4+TIL and P125CD8+TIL cell lines | miR-1908 was found to be over-expressed in TW03 (EBV+) or TW03 (EBV–) cells | –               | [10]       |
| Non-small cell lung cancer | AKT1S1 and RP-pS3 pathway | HBE, SK-MES-1, A549 and NCI-H460 | ↑↑ miR-1908: ↓ Proliferation via targeting AKT1S1 | Tumor suppressor | [9]        |
| Osteosarcoma        | SRSF3/miR-1908-5p/NKIRAS2 axis and NF-κB pathway | U2OS      | ↑↑ miR-1908–5: ↑ proliferation, migration, and invasion via targeting NKIRAS2 | Oncogenic        | [11]       |
|                     | PTEN                               | 143B, U-2 OS, MG-63 and Saos-2, and hFOB 1.19 | ↑↑ miR-1908–5: ↑ proliferation, migration, and invasion | Oncogenic        | [12]       |
| Ovarian cancer      | –                                 | A2780, and SK-OV-3 | ↑↑ miR-1908–5: ↓ cell viability | Tumor suppressor | [13]       |
| Prostate cancer     | SRM                                | 22Rv1, PC3 and PC-3 M-luc-C6 | miR-1908/ SRM axis could control secretion of EVs in prostate cancer | –               | [14]       |
In ovarian cancer, miR-1908-5p has been among miRNAs that predict progression free survival of patients [13].

In brief, dysregulation of miR-1908 has been associated with poor prognosis in cervical cancer, glioblastoma, osteosarcoma and ovarian cancer (Table 5).

### Table 2 Function of miR-1908 in non-malignant disorders based on studies in cell lines (∆: knock-down or deletion SD: Sprague–Dawley, RA: Rheumatoid arthritis, NPCs: neural progenitor cells)

| Disease type                     | Interactions                  | Cell lines                       | Function                                                                 | References |
|----------------------------------|-------------------------------|----------------------------------|-------------------------------------------------------------------------|------------|
| Bipolar disorder                 | DLGAP4, GRIN1, STX1A, CLSTN1 and GRM4 | control and bipolar patient iPSC cell lines | Valproate: ↑ miR-1908-5p expression in normal NPCs and ↓ miR-1908-5p expression in NPCs of patients with bipolar disorder | [15]       |
| Myocardial infarction            | TGF-β1 and Smad2/3           | Cardiac fibroblasts from SD neonatal rats | miR-1908 was found to inhibit the Smad2/3 expression via targeting TGF-β1 | [16]       |
| Obesity                          | –                             | hMADS cells and HPA-v            | ↑↑ miR-1908: ↑ proliferation and ↓ adipogenic differentiation A high level of miR-1908 was observed during the adipogenesis | [17]       |
| Obesity                          | IL-6, TNF-α, leptin and resistin | Human visceral preadipocytes     | Levels of miR-1908 expression were found to be increased during the differentiation of human preadipocytes into adipocytes, and be regulated by adipokines | [18]       |
| Renal fibrosis                   | TGF-β1, smad2/3 and MMP-2    | Human primary renal interstitial cells | ↑↑ miR-1908: ↓ expressions of TGF-β1, smad2/3 and MMP-2, and ↓ renal fibrosis process | [19]       |
| Rheumatoid arthritis             | HOTTIP/miR-1908–5p/STAT3 axis | Rheumatoid arthritis synovial fibroblasts | ↑↑ HOTTIP (which sponges miR-1908): ↑ inflammation in RA | [20]       |
| Scar formation post-burn wound healing | Ski                        | Tissues from the dermis of six patients with hypertrophic scars | ↑↑ miR-1908: ↑ fibrosis and scar formation △ miR-1908: ↓ fibrosis and inflammation | [21]       |

### Table 3 Function of miR-1908 in cancer based on studies in animal models

| Tumor Type          | Animal models                  | Results                                                                 | References |
|---------------------|--------------------------------|-------------------------------------------------------------------------|------------|
| Glioblastoma        | 4–6 week-old male BALB/c nude mice | ↑↑ miR-1908: ↑ tumor volume, tumor weight and tumor growth              | [7]        |
| Osteosarcoma        | 4–6 week-old male BALB/c athymic nude mice | ↑↑ miR-1908: ↑ tumor volume and tumor weight                            | [12]       |

### Table 4 Function of miR-1908 in non-malignant conditions based on studies in animal models (SD: Sprague–Dawley)

| Disease Type                     | Animal models                      | Results                                                                 | References |
|----------------------------------|------------------------------------|-------------------------------------------------------------------------|------------|
| Myocardial infarction            | 8–10-week-old male SD rats         | miR-1908 expression was reduced at 4 weeks after myocardial infarction ↑↑ miR-1908: ↓ myocardial fibrosis, and TGF-β1 and Smad2/3 levels | [16]       |
| Renal fibrosis                   | renal fibrosis mouse models        | ↑↑ miR-1908: ↓ renal fibrosis                                           | [19]       |
| Scar formation post-burn wound healing | male SD rats                   | ↑↑ miR-1908: ↑ scar formation                                           | [21]       |

**Dysregulation of miR-1908 in clinical samples in non-malignant conditions**

miR-1908 has been among miRNAs being under-expressed in depression episodes of the bipolar disorder compared with remission state. This study has suggested miR-1908 one of the most promising
Table 5  Results of studies that reported dysregulation of miR-1908 in clinical samples from cancers (ANCTs: adjacent non-cancerous tissues, OS: overall survival, DFS: disease-free survival, TNM: tumor node metastasis, PFS: progression-free survival, HGSOC: high-grade serous ovarian carcinoma)

| Tumors                      | Samples                                                                 | Expression (Tumor vs. Normal) | Kaplan–Meier analysis (impact of miR-1908 up-regulation) | Univariate/Multivariate cox regression | Association of miR-1908 expression with clinical characteristics | Reference |
|-----------------------------|-------------------------------------------------------------------------|-------------------------------|----------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------|-----------|
| Breast cancer               | TCGA dataset 50 pairs of tumor tissues and ANCTs 60 breast cancer patients compared to 60 healthy controls | Up (Younger breast cancer patients and those with HER2-positive tumors had a higher levels of this miRNA) | – – | – | age and her-2 status | [5] |
| Cervical cancer             | GSE63514 36 pairs of tumor tissues and ANCTs | Up | Shorter OS | – | – | [6] |
| Chordomas                   | 3 chordomas tissues and 3 notochord tissues | Down | – | – | – | [22] |
| Glioblastoma                | 47 glioma patients and five normal brain samples | Up | Shorter OS and DFS | – | – | [7] |
| Glioma                      | GEO and TCGA databases 10 NPC patients and 10 healthy controls | Up | Shorter OS and DFS | – | – | [8] |
| Nasopharyngeal carcinoma    | 212 pairs of tumor tissues and ANCTs | Up | Shorter OS | – | – | [10] |
| Osteosarcoma                | 46 osteosarcoma samples and 9 normal muscle samples | Up | Shorter OS | – | – | [12] |
| Ovarian cancer              | TCGA dataset (491 patients with OC) | Down | Better OS and DFS | miR-1908 expression level was found to be an independent predictor of OS of patients with OC and its expression was associated with age | – | [24] |
| Ovarian cancer              | 175 patients with HGSOC GSE106817 | Down in HGSOC | – | miR-1908-5p was found to be an indicator of PFS | – | [13] |
| Ovarian cancer              | 15 platinum-sensitive ovarian cancer patients and 15 platinum-resistant ovarian cancer patients | Up in platinum-resistant patients | – | – | – | [25] |
miRNAs for diagnosis of depression phase of this disorder [26]. Besides, miR-1908 has been among differentially expressed miRNAs between pre-stroke and post-stroke phases in diverse subtypes of ischemic stroke. Moreover, miR-1908 showed significant diagnostic values in both large artery atherosclerosis and lacunar infarct patients [27]. Table 6 shows the results of research projects that revealed dysregulation of miR-1908 in clinical samples from non-malignant conditions.

Wohlers et al. have analyzed miRNA expression quantitative trait loci among 115 GWAS regions linked with inflammatory disorders. Their comprehensive functional fine-mapping has demonstrated two independent GWAS regions associated with autoimmune diseases risk SNPs with important impacts on miRNA expression. These regions have been shown to influence expression of miR-1908-5p and have been related to SNPs associated with Crohn’s disease (rs102275) and rheumatoid arthritis (rs968567) [28].

**Discussion**

miR-1908 has been shown to contribute in the pathoetiology of several disorders through targeting important signaling pathways, namely PTEN, AKT/FOXO3a and AKT/mTOR, SPRY4/ RAF1, RP-p53 and NF-κB pathways. The majority of studies have indicated an oncogenic role for miR-1908. However, this miRNA has been shown to act as a tumor suppressor in chordoma, lung cancer and ovarian cancer.

Notably, dysregulation of miR-1908 has been associated with poor prognosis in cervical cancer, glioblastoma, osteosarcoma and ovarian cancer. However, the diagnostic role of miR-1908 has not been fully investigated in the context of cancer.

miR-1908 has been among miRNAs that could be used as diagnostic markers in two neuropsychiatric conditions, i.e. bipolar disorder and ischemic stroke. This miRNA has a putative function in fibrotic conditions as well. This function is most probably exerted through modulation of TGF-β signaling.

Taken together, miR-1908 participates in the pathogenesis of different types of cancers, as well as a variety of non-malignant conditions such as bipolar disorder, myocardial infarction, obesity, renal fibrosis, rheumatoid arthritis and scar formation. However, data regarding its participation in each condition is based on few investigations. Thus, additional studies are required for verification of these results. Moreover, conduction of further association studies in different populations is necessary to validate the observed associations between miR-1908 SNPs and hematological indexes, serum metabolite levels, neuroimaging measurement, brain volume measurement, asthma and bipolar disorder.

**Future perspectives**

miR-1908 is a candidate for design of novel therapeutic approaches for a wide array of human disorders. Establishment of these kinds of therapies needs comprehensive assessment of its expression in diverse steps of pathogenic events, particularly in cancers. Safety issues and effective transport of miR-1908-modulating therapies into the target cells are the main issues in this regard. These issues should be solved through application of these methods in animal models.

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**Author contributions**

SGF wrote the manuscript and revised it. MT supervised and designed the study. TK, MS and BMH collected the data and designed the figures and tables. All authors read and approved the final manuscript.

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**Table 6** Dysregulation of miR-1908 in clinical samples from non-malignant conditions (UP: unipolar disorder, BP: bipolar disorder)

| Disease type                  | Samples                                                                 | Expression (Disease vs. Normal)                                                                 | References |
|-------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------|
| Bipolar disorders             | 17 UP and 15 BP patients                                                | Down in bipolar disorder patients in comparison to remission phase                             | [26]       |
| Ischemic stroke               | 13 normal control subjects (NCs), 23 cardioembolism (CARD), 26 cases of large artery atherosclerosis (LAA), 27 cases of lacunar infarct (LAC), and 11 cases of stroke of undetermined etiology (SUE) | Down in LAA, LAC, and SUE patients but not in CARD patients                                    | [27]       |
| Obesity                       | 16 human adipose tissues of obese cases and 12 matched normal tissues    | Down in subcutaneous, up in visceral tissues of obese patients                                 | [17]       |
| Scar formation post-burn wound healing | Tissue from 46 patients with deep second-degree burns and hypertrophic scarring | Up in burn-wounded skin compared with adjacent normal skin, down when the wound was healing and then increased during scar development | [21]       |
Availability of data and materials
The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent of publication
Not applicable.

Competing interests
The authors declare they have no conflict of interest.

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