Systematic Review

# Determining The Role of MicroRNAs in Self-Renewal, Metastasis and Resistance to Drugs in Human Gastric Cancer Based on Data Mining Approaches: A Systematic Review

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Abstract

Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide. The major problems of patients with GC are the lack of proper response to the treatment, drug resistance and metastasis attributed to the presence of a subpopulation of cells inside the tumour that are called cancer stem cells (CSCs). In addition, deregulation of microRNAs (miRNAs) has been reported in different stages of GC. The aim of the present study is to determine and introduce miRNAs that contribute to regulation of stemness, metastasis and drug resistance in GC. A systematic review, we conducted data mining of available datasets and a review of previous studies to select miRNAs that target stemness, epithelial-mesenchymal transition (EMT) and drug resistance. All selected miRNAs were analysed by R software to find a common miRNA target for all three processes. Then, the target prediction of miRNAs and their related signalling pathways were obtained by using bioinformatics tools, ONCO.IO and KEGG databases, respectively. We identified seven miRNAs (miR-34a, miR-23a, miR-27a, miR-30a, miR-19b, miR-107, miR-100) from our searching approach. These miRNAs regulate pathways that contribute to stemness, EMT and drug resistance in GC. Four (miR-34a, miR-23a, miR-30a, and miR-100) had significant interactions with each other and 52 target genes among them, from which *MYC, CDK6, NOTCH1, NOTCH2, SIRT1, CD44, CD24,* and *AXL* were involved in the regulation of several biological processes. These data suggest that the three significant properties can be regulated by common miRNAs (hsa-miR-34a, hsa-miR-23a, hsa-miR-30a and hsa-miR-100). Hence, targeting selected miRNAs or their targets might be helpful to stop tumour growth and metastasis development, and increase tumour sensitivity to chemotherapy agents. This signature can also be assumed for early detection of metastasis or drug resistance. However, there should be additional experimentation to validate these results.

***Keywords:*** Drug Resistance, Gastric Cancer, Metastasis, MicroRNA, Stem Cells

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## Introduction

Gastric cancer (GC) ranks as the fifth most common cancer worldwide (1) and the second most common cancer among Iranian men (2). The rate of GC is estimated at 18.7% per 10,000 males and 11.1% per 10,000 females in Iran (3). The major problems of patients with GC include the lack of a proper response to treatment, drug resistance, and metastasis that leads to a rapid increase in mortality among patients. Recently, cancer stem cells (CSCs) are proposed to be a cause for tumour growth, invasion, recurrence, metastasis potential, and resistance to traditional therapies (4). Most treatments have the capability to eliminate cancer cells but cannot eradicate CSCs (5). Despite the advances in different types of gastric adenocarcinoma treatments, the survival rate of patients is not satisfactory. Although there is enhanced detection of GC, the need exists to develop novel detection kits for early detection of GC (6), detect drug resistance in patients before or after chemotherapy and find those who are at increased risk for metastasis.

microRNAs (miRNAs) are small, non-encoding RNA molecules, 18-24 nucleotides in length. They can bind to the target region of 3′-untranslated regions (3′-UTR) and control gene expressions at the post-transcriptional level by messenger RNA (mRNA) degradation or inhibition of protein translation (7, 8). They are known as oncogenes or tumour suppressors that can target several genes simultaneously (9). miRNAs have a stable structure and more than 50% of the miRNA genes are located in genomic regions associated with cancer (10). Thus, they are considered promising tools for detection of any stage of cancer development and cancer treatment (11). Likewise, miRNAs can control metastasis development through the expressions of a large number of target genes (12), regulation of self-renewal property and resistance to

conventional treatments (13, 14).

Recently, there is a tremendous demand for analysis and interpretation of large volumes of biological data. Hence, bioinformatics studies are analysis tools that help to store, organize, and analyse high-throughput data volumes. Clinical data mining techniques have made remarkable contributions to medical and clinical sciences (15). The overall aim of the present study is to find miRNAs that target stemness, epithelial-mesenchymal transition (EMT) and drug resistance in GC and identify target genes that are effective in this regulation. Understanding the mechanism of regulation by miRNAs, which target three important regulatory pathways in GC, can help with early detection of treatment-resistant patients and those at risk for metastasis following chemotherapy.

## Materials and Methods

### Search strategy

In this systematic review, we initially designed a systematic review to assess the stemness-regulating miRNAs. Relevant published papers were collected through a PubMed search engine (https://www.ncbi.nlm.nih.gov/). Keywords such as "stem cell" or "sphere" or "side population (SP) cell" and "miRNA profile" or "microRNA profile" and "gastric cancer" were used. The duplicated papers or papers without any information about GC stem cells (GCSCs) or miRNAs were excluded.

Next, in order to obtain metastasis-regulating miRNAs, the COREMINE database (https://www.coremine.com/), as a text mining algorithm, was used to search keywords that included "metastasis," "gastric cancer", and "miRNA". In the third step, keywords, such as "gastric cancer", "drug resistance", and "miRNA" were chosen in the CORMINE to acquire a list of drug resistance-regulating miRNAs. Finally, R programming language (version 3.6.1) was used for the identification and analysis of drug resistance/metastasis-regulating miRNAs based on the text mining method.

### microRNA target

miRNAs have a deregulated expression in various types of cancers and might influence cell signalling pathways. Putative miRNA targets are essential to discover relevant pathways and they were identified by the ONCO.IO database (https://onco.io/). The Enrichr database (https://amp.pharm.mssm.edu/Enrichr/) was used for further enrichment analysis, along with KEGG 2015 (https://www.genome.jp/kegg/) to obtain the top ten significant pathways regulated by the miRNA target genes. The role of each miRNA target, such as proliferation, drug resistance, apoptosis, invasion, and metastasis was identified in cellular processes regulation.

### microRNA-target gene network

As described earlier, the function of miRNAs is determined through their target genes. Hence, we created a regulatory network model to illustrate a better concept for miRNA-gene or miRNA-protein interactions through the ONCO.IO database.

The Ethical Committee of Royan Institute reviewed and approved the study (IR.ACECR.ROYAN.1396.230).

## Results

In the present study, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) protocols, we reviewed 138 papers after searching in PubMed. In the first screening, 31 papers were excluded because of a lack of relevance in the title and abstract, and low citation rates. In the second screening, 22 papers were irrelevant to GCSCs and miRNAs (Fig.1). We did not include any meta-analyses and review papers in this study. Finally, 21 studies were chosen and assessed, which pertained to 191 miRNAs involved in regulating stemness features of GC (Table S1, See Supplementary Online Information at www.celljournal.org).

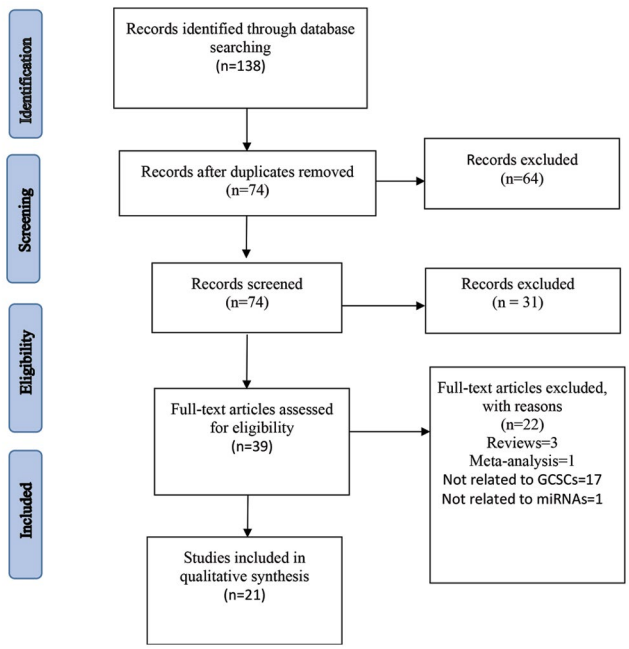


**Fig.1:** Search strategy flowchart of the systematic study derived from PubMed database following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P). GCSC; Gastric cancer stem cell and miRNA; microRNA.

In the second and third steps, 161 and 57 miRNAs were evaluated for metastasis (Table S2, See Supplementary Online Information at www.celljournal.org) and drug resistance properties (Table S3, See Supplementary Online Information at www.celljournal.org) respectively, through the CORMINE database. We determined that there were seven common miRNAs involved in these three properties (miR-34a, miR-23a, miR-27a, miR-30a, miR-19b, miR-107, miR-100) (Fig.2).

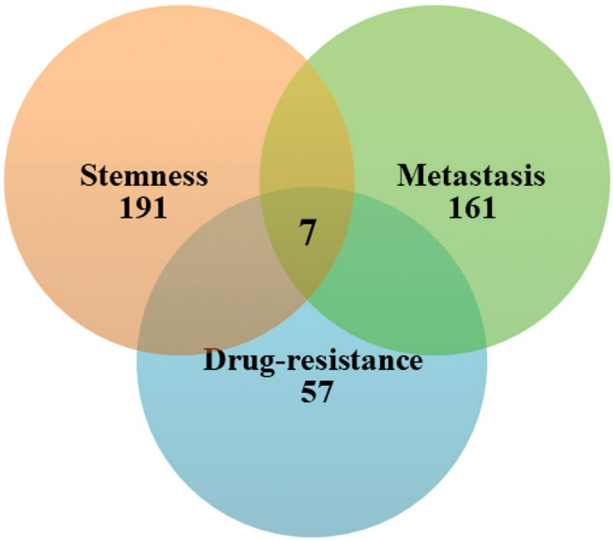


**Fig.2:** Venn diagram that shows the common microRNAs (miRNAs) in all three pathways.

## Investigation of the regulatory network for the microRNA target genes

The ONCO.IO database was used to obtain a regulatory network of seven effective stemness-regulating miRNAs, metastasis, and drug resistance. The results indicated that miR-34a, miR-23a, miR-30a and miR-100 showed significant interactions with each other, and a network of target genes (Fig.3). These target genes have the greatest effect on regulating biological processes of invasion, proliferation, migration, and apoptosis. Table 1 lists the effects of the miR-34a, miR-23a, miR-30a, and miR-100 targets in regulating these biological processes.

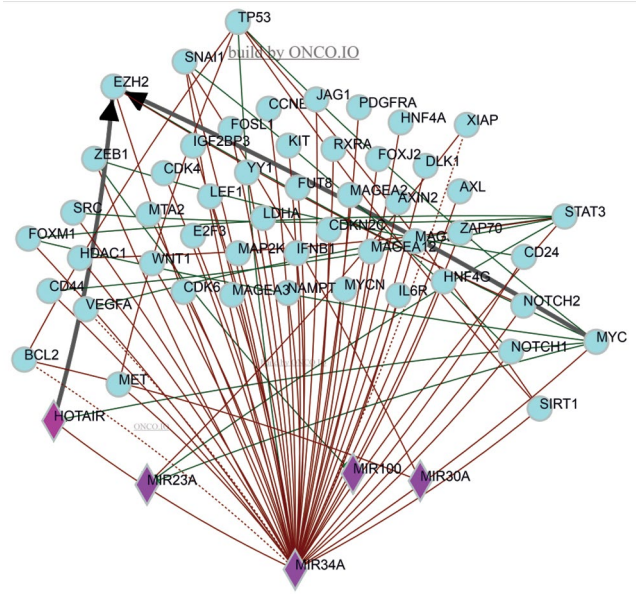


**Fig.3:** A network of differential expression of four microRNA (miRNA) target genes. Circle and rhombic forms represent target genes and miRNAs, respectively. The red and green arrows indicate inhibitors and activators, respectively. The thick black arrow shows the interaction between two genes.

**Table 1:** Performance of 52 targeted target genes of four microRNAs (miRNAs) in the regulation of important biological processes. Some of these genes interact with the regulation of several bio-processes

| Process | Number | Gene |
|---|---|---|
| Invasion | 18 | *SNAI1, MYC, MET, NOTCH1, NOTCH2, CDK6, JAG1,CDK6, STAT3, FOSL1, DLK1, KIT, CD24, SRC, IL6R, HOTAIR, HNF4G, FUT8* |
| Proliferation | 15 | *AXL, MYC, MET, NOTCH1, NOTCH2, CDK6, MAP2K1, SIRT1, DLK1, CD44, HOTAIR, HNF4G, HDAC1, IGF2BP3, EZH2* |
| Migration | 10 | *SNAI1, MYC, MET,YY1, FOSL1 , KIT, CD44, CD24, SRC, FUT8* |
| Apoptosis | 10 | *TP53, AXL, MET, CDK6, SIRT1, DLK1,HDAC1, XIAP, IGF2BP3, BCL2* |
| Chemoresistance | 6 | *AXL, SIRT1, MAGEA2, MAGEA3, MAGEA6, MAGEA12* |
| Metastasis | 5 | *YY1, CDK6 , NOTCH2, NOTCH1, CD44,* |
| EMT | 3 | *STAT3 ,IL6R, CD24* |
| Stemness | 2 | *MYC, CD24* |

EMT; Epithelial-mesenchymal transition.

**Table 2:** A list of microRNA (miRNA) targets based on relative position

| Upstream genes | | | Downstream genes | | | |
|---|---|---|---|---|---|---|
| *ZEB1* | *HNF4A* | *MTA2* | *MET* | *MAP2K1* | *FOSL1* | *IFNB1* |
| *TP53* | *AXL* | *WNT1* | *YY1* | *AXIN2* | *MAGEA2* | *ZAP70* |
| *STAT3* | *MYCN* | *LDHA* | *NOTCH1* | *SIRT1* | *MAGEA3* | *DLK1* |
| *EZH2* | *CCNE2* | *BCL2* | *JAG1* | *CDKN2C* | *FUT8* | *KIT* |
| *HOTAIR* | *CDK4* | *XIAP* | *NOTCH2* | *PDGFRA* | *FOXJ2* | *CD24* |
| *SNAI1* | *E2F3* | *VEGFA* | *HDAC1* | *LEF1* | *MAGEA6* | *CD44* |
| | *HNF4G* | *MYC* | *CDK6* | *NAMPT* | *MAGEA12* | |
| | *RXRA* | *IL6R* | *IGF2BP3* | *FOXM1* | *SRC* | |

### Regulation of cell signalling pathways by microRNAs in cancer development

A list of target genes for *miRNAs (miR-34a, miR-23a miR-30a, miR-100)* was obtained using the ONCO.IO database to find signalling pathways regulated by miRNAs. The results demonstrated that 52 genes are regulated by four miRNAs (Table 2). Enrichr database was used to investigate these target genes. Consequently, the KEGG database was used to analyse the functional pathways of four miRNAs. These miRNAs are significantly involved in the top ten pathways that regulate cell signalling, including pathways in cancer, miRNAs in cancer, the PI3K-Akt signalling pathway, hepatitis B, small cell lung cancer, bladder cancer, pancreatic cancer, melanoma, central carbon metabolism in cancer, and the thyroid hormone signalling pathway (Table 3). Pathways with the strongest P values were analysed and it was determined that most of these are cancer-dependent.

**Table 3:** Targeted signalling pathways by seven selected microRNAs (miRNAs) according to the highest P value

| Rank | Signalling pathway | P value |
|---|---|---|
| 1 | Pathways in cancer | 8.134e-18 |
| 2 | miRNAs in cancer | 2.612e-18 |
| 3 | PI3K-Akt signalling pathway | 4.343e-12 |
| 4 | Hepatitis B | 4.343e-12 |
| 5 | Small cell lung cancer | 2.711e-11 |
| 6 | Bladder cancer | 2.421e-10 |
| 7 | Pancreatic cancer | 6.671e-9 |
| 8 | Melanoma | 8.983e-9 |
| 9 | Central carbon metabolism in cancer | 6.671e-9 |
| 10 | Thyroid hormone signalling pathway | 8.983e-9 |

## Discussion

miRNAs have a significant effect on regulation of gene expression and they have their own distinct expression patterns in various cancers. Therefore, the identification of miRNA biomarkers might provide tremendous opportunities for the sensitisation of tumour cells to targeted therapeutic agents in order to prevent cancer metastasis (10).

The results of some biological and clinical trials support miRNAs regulation in GC. However, a few systematic studies have focused on novel miRNA candidates that possess all three effective properties in GC development. In this study, miRNAs that regulate stemness, drug resistance, and metastasis features were selected by bioinformatics approaches (database sources and R programming language) and systematic literature reviews. Bioinformatics algorithms show significant potential in medical research. These tools help researchers understand the biological processes in different disorders and predict disease-prone genes. They also can reduce a considerable amount of search space of datasets and detect the highest statistical significance datasets (15). The integration of miRNA profiles and their targets with computational analysis tools helps to investigate the role of miRNAs in the development of metastatic cancer and their potential role as agents in cancer treatment (16).

Based on the present study, six miRNAs (miR-100, miR-34a, miR-23a, miR-27a, miR-30a, and miR-19b) were obtained that contributed to regulation of stemness, metastasis and drug resistance in GC. These miRNAs can potentially be used to induce the sensitivity of GC cells to chemotherapy. Six of the seven candidate miRNAs (miR-23a, miR-27a, miR-30a, miR-19b, miR-107 and miR-100) are overexpressed in GC. Interestingly, all of the predicted miRNAs were previously reported to play pivotal roles in stem cell-like phenotype and drug resistance in GC (17-20). It is proposed that these miRNAs act as an oncomiR, which might have a carcinogenic function. However, many other miRNAs have reduced expressions in various types of cancers and they act as tumour suppressors. Among this set, both miR-34a and miR-100 have low expressions in GC and can inhibit invasion, metastasis and the possibility of tumour relapse (21, 22).

Four miRNAs (miR-34a, miR-23a miR-30a, miR-100) play an important role in interacting with target genes. They regulate important cellular processes as well as signalling pathways. Among the four major miRNAs, miR-34a regulates a variety of target genes involved in promoting cell death by (SP-4-2)-diamminedichloroplatinum (cisplatin) with involvement of the PI3K/Akt/survivin signalling pathway (23). Excessive expression of miR-34a leads to enhanced sensitivity of GC cells exposed to cisplatin-based chemotherapy. Overexpression of miR-34a can inhibit invasion and induce apoptosis by inhibiting the *PI3K/Akt* signalling pathway in the SGC-7901 GC cell line (24, 25). miR-34a, by targeting the *NOTCH, HMGA2* and *BCL2* genes, can control self-renewal and survival of CSCs in GC (17, 26).

miR-23a is located in the miR-23a~27a~24-2 cluster and its overexpression promotes acute lymphoblastic leukaemia, acute myeloid leukaemia, and pancreatic cancer. It appears to increase significantly in GC compared to normal tissues and is recognized as an oncomiR in tumour malignancy (18). It can also regulate the sensitivity of GC cells to chemotherapy by inhibiting the *ATG12* and *HMGB2* genes, which are associated with autophagocytosis (19). Inhibition of *PTEN* gene by miR-23a leads to activation of Akt/ERK and EMT related pathways in GC cells; thereby it causes an induction of proliferation in GC cells and tumour growth in mouse models (27).

miR-30a can act as an oncomiR in GC by regulating the P53-mediated mitochondrial apoptotic pathway (27). It can also reduce the multidrug resistance (MDR) of GC cells and acts as an inhibitor of EMT in other cancer cells (28).

Overexpression of miR-100 can inhibit cell proliferation in GC cells by targeting BMPR2 and CXCR7 (29, 30). Moreover, it can promote apoptosis by cisplatin (2 μg/ml) (29). Since both BMPR2 and CXCR7 have a role in promoting invasion and tumour metastasis in cancers, miR-100 might regulate the metastasis potential in GC (29, 30).

Enrichment analysis of the miRNA target genes by Enrichr and KEGG showed that the most significant pathways were associated with cancer. The PI3K/Akt signalling pathway has a specific role in gastric adenocarcinoma treatment, as personalized medicine. The role of miRNAs in GCSCs has been shown by regulation of the PI3K/Akt pathway (31, 32).

## Conclusion

Overall, the results of systematic literature reviews and data mining showed that the three important properties involved in GC could be regulated by Six miRNAs (miR-100, miR-34a, miR-23a, miR-27a, miR-30a, and miR-19b). Among them, miR-34a, miR-23a, miR-30a and miR-100 were the more relevant in regulating the three features associated with cancer development. Hence, bioinformatics analysis could be a useful approach to predict miRNAs or their targets that could halt tumour growth and metastasis development, and increase tumour sensitivity to chemotherapy agents. Our miRNA signature could be assumed for early detection of metastasis or drug resistance. However, additional studies should be conducted to validate our findings.

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## Authors' Contributions

M.A.; Analysed the data, designed the manuscript structure, and wrote the manuscript. M.T.; Validation of data and conceived the presented idea. M.E.; Contributed to the study concept and design, and final approval of the manuscript. All authors read and approved the final manuscript.

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