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REVIEW ARTICLE

# miRNA Regulation of Glutathione Homeostasis in Cancer Initiation, Progression and Therapy Resistance

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**Abstract:** Glutathione (GSH) is the most abundant antioxidant that contributes to regulating the cellular production of Reactive Oxygen Species (ROS) which, maintained at physiological levels, can exert a function of second messengers in living organisms. In fact, it has been demonstrated that moderate amounts of ROS can activate the signaling pathways involved in cell growth and proliferation, while high levels of ROS induce DNA damage leading to cancer development. Therefore, GSH is a crucial player in the maintenance of redox homeostasis and its metabolism has a role in tumor initiation, progression, and therapy resistance. Our recent studies demonstrated that neuroblastoma cells resistant to etoposide, a common chemotherapeutic drug, show a partial monoallelic deletion of the locus coding for miRNA 15a and 16-1 leading to a loss of these miRNAs and the activation of GSH-dependent responses. Therefore, the aim of this review is to highlight the role of specific miRNAs in the modulation of intracellular GSH levels in order to take into consideration the use of modulators of miRNA expression as a useful strategy to better sensitize tumors to current therapies.

**Keywords:** Cancer, chemoresistance, epigenetic mechanisms, glutathione homeostasis, miRNA, reactive oxygen species.

## 1. INTRODUCTION

During metabolic processes, all aerobic cells produce Reactive Oxygen Species (ROS) which act as signalling molecules at physiological levels but, when their amount exceeds the cell antioxidant response, physio-pathological (*i.e.* aging) and pathological (*i.e.* cancer) events occur. In both cancer and healthy cells, the maintenance of the redox equilibrium is crucial in order to guarantee cell survival [1, 2]. All cells are able to counteract ROS overproduction by means of enzymatic and non-enzymatic antioxidant systems, and, among these, glutathione (GSH) plays a fundamental role. GSH is a multifunctional tripeptide (γ-glutamyl-cysteinyl-glycine) involved in several metabolic and cellular processes such as cell differentiation, proliferation, and death [3, 4] and also in all phases of cancer progression and in the acquisition of treatment resistance [5-7].

The maintenance of adequate intracellular GSH levels is the result of the coordinated action of several enzymes that contribute to its synthesis (*i.e.* glutamate-cysteine-ligase, GCL and glutathione-synthetase, GSS), its reduction from GSSG (glutathione-reductase, GR), degradation (γ-glutamyl-transferase, γ-GT), or its employment (glutathione-S-transferase, GST and glutathione peroxidase, GPx) [5].

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GCL which catalyzes the chemical bond of L-glutamate with cysteine, the rate-limiting reaction in GSH biosynthesis, was found to be down-regulated in ectopic endometriosis lesions [8], while GSS, catalyzing the reaction between γ-glutamyl-cysteine and glycine leading to GSH formation, was over-expressed in colon cancer [9]. GR, which catalyzes the reduction of GSSG to GSH, was down-regulated in glioblastoma and meningioma [10] while γ-GT, catalyzing extracellular GSH degradation leading to the formation of glutamate and cysteine, was up-regulated in gastric cancer [11], sarcoma, leukaemia, melanoma [12], Hepatocellular Carcinoma (HCC), and breast cancer [13, 14].

Among GSH-dependent enzymes, GST, a detoxifying enzyme that catalyzes the reaction of endogenous/exogenous substrates with GSH, was up-regulated in several cancers that have become chemoresistant such as breast cancer [15], Hodgkin's lymphoma [16], and neuroblastoma [6, 17].

Moreover, GPxs are a family of enzymes that are able to reduce free hydrogen peroxide to water and lipid hydroperoxides to their corresponding alcohols. It has been demonstrated that GPx4 over-expression characterizes ovarian cancer, melanoma, and diffuse large B-cell lymphoma [18, 19] and it is crucially involved in the acquisition of chemoresistance and in cancer relapse [19-21] probably by limiting the formation of lipoperoxides responsible for inducing ferroptosis [19, 20].

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**Table 1. MiRNAs involved in the regulation of GSH homeostasis in cancer.**

| MiRNA | Target | Cancer | Refs. |
|---|---|---|---|
| miRNA-18a | GCL | Hepatocellular carcinoma | [25] |
| | | Prostatic cancer | [26] |
| miRNA-433 | | Liver cancer | [27] |
| | | Ovarian cancer | [28] |
| | | Colon cancer | [29] |
| miRNA-27a/b | | Hepatocellular carcinoma | [30] |
| miRNA-125b | GSS | Chronic lymphocytic leukemia | [31] |
| miRNA-214 | GR | Breast cancer | [32] |
| | | Lung adenocarcinoma | [33] |
| | | Colorectal cancer and Cervical cancer | [34] |
| | | Lung cancer | [35] |
| | | Kidney cancer | [36] |
| miRNA-22 | γ-GT | Hepatocellular carcinoma | [37] |
| | | Colorectal cancer | [38] |
| | | Gastric cancer | [39] |
| | | Prostatic cancer | [40] |
| miRNA-133 | GST | Bladder cancer | [41] |
| | | Ovarian cancer | [42] |
| | | Lung cancer | [43] |
| miRNA-513-a-3p | | Lung cancer | [44] |
| miRNA-153 | GPx | Glioblastoma | [45] |
| miRNA-185-5p | | Colorectal cancer | [46] |
| | | Hepatocellular carcinoma | [47] |
| miRNA-17-3p | | Prostatic cancer | [48] |
| miRNA-26b | xCT | Breast cancer | [49] |
| | | Colorectal cancer | [50, 51] |
| miRNA-375 | | Squamous cell carcinoma | [52, 53] |
| miRNA-27 | | Breast cancer | [54] |
| miRNA-124 | ΔNp63 | Colorectal cancer | [55] |
| miRNA-527<br>miRNA-665 | | Osteosarcoma | [56] |
| miRNA-28 | Nrf2 | Breast cancer cells | [57] |
| miRNA-27a<br>miRNA-153 | | Neuroblastoma cells | [58] |
| miRNA-432-3p | | Esophageal squamous cell carcinoma | [59] |

Interestingly, it has been shown that the day-time variation of GSH levels can be regulated by several miRNAs and this circadian rhythm is linked to various human diseases related to oxidative stress [22]. miRNAs are short double-stranded RNAs able to regulate gene expression by linking themselves to the complementary RNAs [23]. In relation to their role in cancer, miRNAs are divided into two classes: the oncogenic miRNAs, which target oncosuppressor genes, and Tumor-Suppressive (TS)-miRNAs targeting oncogenes.

Therefore, the aim of this review is to focus on the role of specific miRNAs in the regulation of GSH homeostasis in cancer initiation, progression, and therapy resistance.

## 2. ROLE OF MIRNAs IN THE ALTERATIONS OF GSH HOMEOSTASIS IN CANCER

Despite the synergistic role played by miRNAs and the cell redox state having been well-documented in the pathogenesis of several diseases [24], the specific role of miRNAs in GSH homeostasis has only been partially investigated. In Table **1**, the miRNAs involved in the most important steps of GSH homeostasis are listed [25-59].

### 2.1. MiRNAs Involved in the Regulation of GSH Synthesis and Employment

The over-expression of miRNA-18a, a Myc-regulated miRNA belonging to the miRNA-17-92 cluster [60-62], has

been demonstrated to induce a decrease in the GCL expression, playing a role as an oncogene in HCC [25]. Moreover, miRNA-433 down-regulated the expression of both catalytic (GCLC) and regulatory (GCLM) subunits of GCL by an Nrf2-independent mechanism [63] while miRNA-27a/b modulated GCL expression in an Nrf2-dependent manner [64].

It has been found that GSS levels are inversely related to those of miRNA125-b whose expression is down-regulated in chronic lymphocytic leukemia patients, conferring an oncosuppressor role to this miRNA [31].

The over-expression of miRNA-214 has been demonstrated to reduce the expression of GR causing a condition of oxidative stress. In this regard, Feng *et al*. reported that miRNA-214 over-expression is related to a poor prognosis in several cancers [65].

In addition, the γ-GT expression is inhibited by miRNA-22 in HCC [37] and GST is inhibited by miRNA-133b, triggering apoptosis in bladder cancer [41] and sensitizing ovarian [42] and lung cancers [43] to chemotherapeutic drugs. Similar action has been described for miRNA-513-a-3p that sensitizes lung cancer to cisplatin-induced cytotoxic effects by down-regulating GST [44].

In regards to the role of miRNAs in the modulation of GPx expression, it has been observed that the miRNA-153/Nrf2/GPx1 pathway regulates the radiosensitivity of glioblastoma stem cells by favoring cell differentiation *via* ROS-dependent activation of the p38MAPK pathway [45]. A modulator of GPx2 expression is miRNA-185-5p that acts as an oncosuppressor in colorectal cancer: its over-expression is inversely correlated with the expression of the Stromal Interaction Molecule 1 (STIM1), a protein able to facilitate the metastatic process [46]. Moreover, miRNA-17-3p has been found to suppress the tumorigenicity of prostate cancer cells by inhibiting the expression of GPx2, manganese superoxide dismutase, and thioredoxin reductase [48].

Furthermore, xCT or Solute Carrier Family seven-member eleven (SLC7A11) is a cystine/glutamate antiport that regulates the cysteine influx favoring GSH biosynthesis [66] and is stabilized in the cell membrane by CD44v, a known cancer stem cell marker [67]. It has been found that the xCT expression level is inversely correlated with that of miRNA-26b in human breast cancer cell lines and specimens [49]. In addition, miRNA-375 over-expression, by down-regulating the xCT expression, inhibited the proliferation and invasion and enhanced the radiosensitivity of oral squamous cell carcinoma also *via* Insulin-Like Growth Factor-1 Receptor (IGF-1R) inhibition [52, 53]. Similarly, miRNA-27 over-expression has been observed to reduce xCT levels and intracellular GSH amounts, re-sensitizing breast cancer cells resistant to cisplatin [54].

The expression of the genes, coding for the above-reported GSH-related enzymes, is modulated by ΔNp63 and by Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), two transcription factors involved in cancer initiation and progression. ΔNp63 belongs to the p53 gene family and plays a crucial role as an oncosuppressor [68]. Depending on the promoter that is activated, the transcription of the same gene may produce the full-length transactivation domain (TAp63) or the truncated N-terminus which lacks the transactivation domain (ΔNp63) [69]. ΔNp63 is able to regulate the expression of GCL, GSS, and GPx2, contributing to the increase of the intracellular GSH/GSSG ratio [70].

Furthermore, the transcription factor Nrf2 has a role in the regulation of GSH-related enzymes [71]. Under basal conditions, Nrf2 homeostasis is maintained by Kelch-like ECH-associated protein 1 (Keap1), the endogenous inhibitor of Nrf2 that binds to, and detains Nrf2 in the cytosol, facilitating its ubiquitination and proteasomal degradation [72]. Under oxidative stress conditions, Keap1 undergoes conformational changes that prevent its binding with Nrf2. Therefore, Nrf2 moves into the nucleus where it can modulate the expression of the cytoprotective antioxidant genes [73]. In fact, it has been recently demonstrated that Nrf2 has a two-fold role in the carcinogenic process, acting as an oncogene as well as an oncosuppressor [74]. Moreover, the increase in Nrf2 levels has been related to chemosensitivity in neuroblastoma cells treated with L-Buthionine-Sulfoximine, a GSH-depleting agent, or with Bortezomib, a proteasome inhibitor [75, 76]. In addition, it has been recently demonstrated that the Keap1/Nrf2 pathway drives metabolic reprogramming and increases the sensitivity to the glutaminase inhibitor CB-839 in KRAS-mutant lung adenocarcinoma [77].

In this regard, it has been recently reported that miRNA-144 over-expression inhibited Nrf2 with a consequent reduction of GSH levels [78, 79]. Moreover, the over-expression of miRNA-28, miRNA-27a, and miRNA-153 is accompanied by a reduction of Nrf2 levels by promoting mRNA degradation or by reducing its stability in a Keap1-independent way [57, 58]. In a different way, the over-expression of miRNA-432-3p is able to lower Keap1 levels and consequently to increase Nrf2 activity, contributing to the acquisition of cisplatin resistance in several cancer cells [59]. Therefore, the Nrf2-dependent pathway can be modulated by many miRNAs whose biosynthesis can, in turn, be regulated by Nrf2. In fact, Nrf2-dependent Heme Oxygenase-1 (HO-1) over-expression was able to reduce miRNA biosynthesis by down-regulating DiGeorge Critical Region-8 (DGCR8) which is a protein involved in miRNA maturation [80].

### 2.2. MiRNAs Involved in the Reprogramming of Cancer Cell Metabolism

Moreover, it is necessary to underline that GSH homeostasis is not only regulated by the above-mentioned enzymes but also by the metabolic reprogramming of cancer cells which is characterized by an increase in glycolysis and glutaminolysis in dependence of their ability to have an increased glucose and glutamine uptake [81, 82]. It is important to note that glucose metabolism in cancer cells also occurs *via* the Pentose Phosphate Pathway (PPP) leading to NADPH formation (Fig. **1**) that is crucial to restoring GSH in its reduced form [83]. Moreover, it has been extensively demonstrated that the oncogene Myc (c-Myc and N-Myc) is able to modulate the expression of GLUT1 and glutaminase,

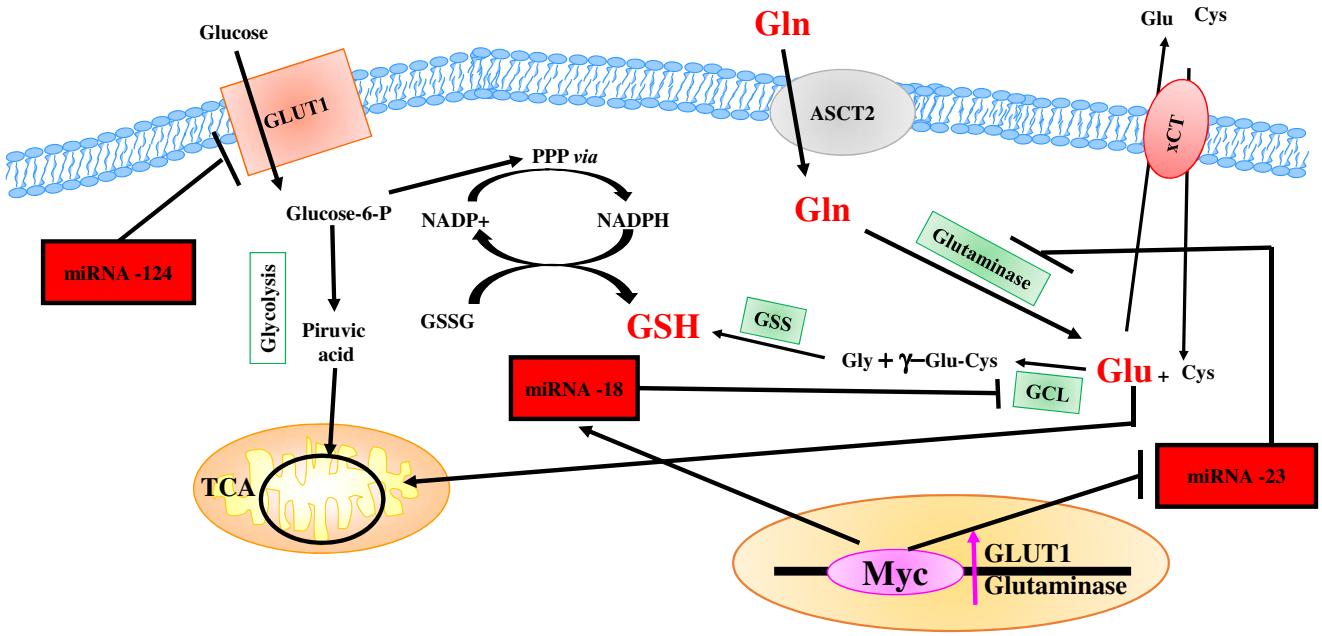


**Fig. (1).** Relationship between modulation of GSH homeostasis and cancer metabolic reprogramming. The metabolic reprogramming, an event that characterizes cancer cells, leads to an increase in both glycolysis and glutaminolysis. This adaptation is due to the ability of cancer cells to facilitate the glucose uptake by increasing the expression of glucose transporters 1 (GLUT1) and increasing glutamate intracellular levels by stimulation of the glutaminase (GLS) activity. However, intracellular glucose is metabolized by glycolysis, but also *via* the Pentose Phosphate Pathway (PPP) which, leading to the formation of NADPH, contributes to maintaining GSH in its reduced form. On the other hand, GSH levels are also due to the action of glutaminase, the enzyme that catalyzes glutamine deamination contributing to the formation of glutamate that can be used either in the Tricarboxylic Acid cycle (TCA) to produce ATP and in GSH biosynthesis. In this network, Myc, which has a central role by directly increasing the gene transcription of GLUT1 and glutaminase, is also able to modulate these genes by regulating the expression of specific miRNAs.

which catalyzes glutamine deamination leading to the formation of glutamate that can then be used either in the Tricarboxylic Acid cycle (TCA) to produce ATP or in GSH biosynthesis (Fig. **1**).

Recent studies reported that N-Myc promotes glutamine catabolism by the selective activation of glutaminase 2 (GLS2) which is able to modulate both oxidative phosphorylation and glycolysis [84]. The GLS2-dependent regulation of glycolysis is probably due to the ability of Nrf2 to modulate the expression of GLUT1 [85] and of many enzymes involved in glycolysis such as lactic dehydrogenase, hexokinase, phosphofructokinase, and enolase [86].

Therefore, the Myc oncogene plays a central role in modulating GSH homeostasis and metabolism in cancer cells (Fig. **1**) [87] and, interestingly, it has been found that it may exert its function also by regulating the processing and the expression of several miRNAs [88]. In fact, the overexpression of miRNA-124 in B-cell lymphoma inhibited the expression of Myc and Bcl-2 [89] and suppressed proliferation and glycolysis in non-small cell lung cancer cells by targeting Akt-GLUT1/hexokinase II [90]. Moreover, elevated levels of Myc in human prostate cancer cells can inhibit miRNA-23a, thus enhancing the expression of GLS, its specific target, and increasing glutamine metabolism [91]. Instead, in Myc-driven liver tumors, miRNA-18 overexpression reduces the expression of GCL, inhibiting GSH synthesis (Fig. **1**) [25].

## 3. MiRNA THERAPY: A PROMISING STRATEGY IN TREATMENT OF CANCER AND IN THE PREVENTION OF CHEMORESISTANCE

The above-mentioned miRNAs involved in GSH homeostasis and metabolic reprogramming could play an oncogenic or oncosuppressor role in several kinds of tumors. In more detail, miRNA-18 acts as an oncogene in prostatic [26] and in breast cancer [92] and, analogously, miRNA-26b in colorectal cancer by stimulating Epithelial-Mesenchymal Transition (EMT) and CSC generation [50].

An oncosuppressor role has been reported for miRNA-433 in liver [27], ovarian [28], and colon cancer [29]; for miRNA-185-5p in HCC [47] and for miRNA-375 in colorectal cancer [51].

Moreover, miRNA-214 acts as an oncogene in breast cancer by modulating the Akt-pathway [32] and in lung adenocarcinoma by facilitating EMT and metastatization [33] whereas it can act as an oncosuppressor in lung [35], kidney [36], colorectal, and cervical cancer by modulating the expression of the high mobility group AT-hook (HMGA), a protein involved in the regulation of cell metabolism [34]. Similarly, also miRNA-22 has a double role: in fact, it can act as an oncogene modulating EMT and reducing E-cadherin levels, thus increasing *in vivo* prostate cancer invasivity [40], while it plays an oncosuppressor role in colorectal [38] and in gastric cancer [39]. *In vivo* and *in vitro* studies demonstrated that miRNA-124 modulates the expression of

**Table 2. MiRNAs targeting GSH homeostasis able to inhibit cancer growth and to counteract therapy resistance.**

| miRNA | Manipulation | Outcome Following Manipulation | Cancers | Refs. |
|---|---|---|---|---|
| miRNA-18a | Downregulation | Radiosensitization<br>Reduction tumor growth<br>Chemiosensitization | NSCLC<br>Prostatic cancer<br>Breast cancer | [92]<br>[26]<br>[93] |
| | Overexpression | Apoptosis, migration inhibition | Colorectal cancer | [94] |
| miRNA-433 | Overexpression | Chemiosensitization<br>Migration and proliferation inhibition | Cervical cancer<br>Bladder cancer, Colon cancer | [95]<br>[29, 96] |
| miRNA-27a/b | Downregulation | Tumor growth inhibition<br>Migration and proliferation inhibition | Breast cancer<br>Multiple myeloma | [97, 98]<br>[99] |
| | Overexpression | Chemiosensitization<br>Migration and proliferation inhibition | Breast cancer<br>Adenocarcinoma | [100]<br>[101] |
| miRNA-125b | Downregulation | Reversion of EMT<br>CSC formation inhibition<br>Apoptosis | Pancreatic adenocarcinoma<br>NSCLC<br>Breast cancer | [102]<br>[103]<br>[104] |
| | Overexpression | Migration and proliferation inhibition<br>CSC formation inhibition<br>Chemiosensitization | Gastric cancer<br>Breast cancer<br>Breast cancer, Gastric cancer,<br>Gallbladder cancer | [105]<br>[106]<br>[107-109] |
| miRNA-214 | Downregulation | Radiosensitization<br>Metastasis inhibition | Osteosarcoma<br>Melanoma, breast cancer | [110]<br>[111, 112] |
| | Overexpression | Radiosensitization<br>CSC formation inhibition<br>Chemiosensitization<br>Migration and tumorigenesis inhibition | Colorectal cancer<br>NSCLC<br>Breast cancer<br>Prostate cancer, Cervical cancer | [113]<br>[114]<br>[115]<br>[116, 117] |
| miRNA-22 | Overexpression | Radiosensitization<br>Chemiosensitization<br>Cancer progression inhibition<br>Migration and proliferation inhibition | Breast Cancer<br>Tongue squamous cell carcinoma<br>Cervical cancer, Acute myeloid leukaemia,<br>Breast carcinoma, Osteosarcoma, prostate<br>cancer, cervical cancer and lung cancer | [118]<br>[119]<br>[120]<br>[121-123] |
| miRNA-133 | Overexpression | Invasiveness and tumorigenesis inhibition | Breast cancer<br>NSCLC | [124]<br>[125] |
| miRNA-513-a-3p | Overexpression | Chemiosensitization | Lung adenocarcinoma | [44] |
| miRNA-153 | Overexpression | Chemiosensitization<br>Tumor growth inhibition | Breast cancer<br>Lung cancer, Breast cancer,<br>Bladder cancer | [126]<br>[127-129] |
| miRNA-185-5p | Overexpression | Chemiosensitization<br>Tumor growth inhibition | NSCLC<br>Breast cancer | [130]<br>[131, 132] |
| miRNA-17-3p | Downregulation | Proliferation inhibition | Colon cancer | [133] |
| | Overexpression | Radiosensitization | Prostate cancer | [134] |
| miRNA-26b | Overexpression | Proliferation inhibition<br>Chemiosensitization | Colon cancer, Breast cancer<br>Laryngeal cancer, Glioma, HCC | [135, 136]<br>[137-139] |
| miRNA-375 | Overexpression | Cancer growth inhibition | Colon cancer, Liver cancer | [140, 141] |
| miRNA-124 | Overexpression | Radiosensitization<br>Tumor growth inhibition | Colorectal cancer, Head and neck carcinoma<br>Prostate cancer, Medulloblastoma | [142, 143]<br>[144]<br>[145] |
| miRNA-665 | Overexpression | Tumor growth and migration inhibition | Ovarian cancer, Osteosarcoma | [146, 147] |
| miRNA-28 | Overexpression | Proliferation inhibition | Renal cell carcinoma | [148] |

ΔNp63 and TAp63, influencing the growth of colorectal cancer [55]. On the other hand, it has been observed that ΔNp63, by directly inhibiting the expression of both miRNA-527 and miRNA-665, stimulates osteosarcoma metastatic dissemination facilitating an EMT response [56].

Considering the role that these miRNAs play in cancer progression, it is possible that the utilization of miRNA mimics or inhibitors can be used to stimulate or inhibit the activity of GSH-related enzymes in order to stop cancer growth and to prevent the onset of chemoresistance.

In fact, as reported in Table **2**, several *in vitro* and *in vivo* studies demonstrated that the over-expression or down-regulation of GSH-related miRNAs is efficacious in counteracting tumor growth and sensitizing cancer cells to different therapeutic approaches, suggesting that the manipulation of these miRNA levels could offer new opportunities to treat cancer patients.

Although the therapeutic relevance of this approach could be remarkable, its efficacy depends on the way in which miRNAs enter the target cells. In fact, since endocytosis does not guarantee an adequate supply of miRNAs, it is fundamental to identify methods that are able to specifically and efficiently "ferry" these miRNAs into the target cells [149].

To this end, several Stable Nucleic Acid-Lipid nanoparticles (SNALP), capable of "ferrying" miRNAs, have been developed. This has led to the formulation of MRX34 which enables the introduction of a miRNA-34 mimic into the cell and which is currently being used in a Phase I clinical trial for primary and secondary liver tumors (NCT01829971).

In another study, it has been recently demonstrated that miRNA-34 encapsulated in hyaluronic acid nanoparticles is able to reduce intracellular GSH levels and Nrf2 expression, thus sensitizing Non-Small-Cell Lung Carcinoma (NSCLC) cells to the cytotoxic effects of cisplatin [150].

An additional therapeutic strategy could be the combination of these miRNAs with chemotherapeutic drugs by loading them into biodegradable polymeric nanocarriers. In this context, it has been reported that micelles formed by miRNA-205 and gemcitabine are able to revert the chemoresistance of pancreatic cancer both *in vitro* and *in vivo* [151]. Other promising results were obtained for glioma by using nanocarriers loaded with the miRNA-21 inhibitor and doxorubicin [152]. Nanoparticles consisting of miRNA-200c and docetaxel have been shown to potentiate the drug efficacy and to counteract cancer growth *in vivo*, by reducing the CD44 expression and increasing E-cadherin [153]. In order to "ferry" miRNAs together with drugs, several nanocarriers have been developed and despite the *in vitro* results being promising, they still need to be validated *in vivo* before being considered for clinical trials [149].

Recently, a new redox-responsive system based on ferrocenium capped-amphiphilic-pillar[5]arene has been formulated and utilized to introduce miRNAs and the associated drug in cancer cells characterized by high GSH levels [154].

## CONCLUSION

The review deals with the role of GSH homeostasis in tumor initiation, progression, and drug resistance and the implication of specific miRNA in changing GSH levels and influencing the pathogenesis and outcome treatment of cancer. Moreover, tumor cells could be sensitized to a specific therapy that, by reactivating oncosuppressor-miRNAs or by inhibiting oncogenic miRNAs, reduces the antioxidant defenses and hinders the metabolic reprogramming, thus preventing CSC generation and inducing apoptosis.

In fact, the results obtained in combining drugs and miRNAs are promising and the research that is aimed at finding GSH-related miRNAs will be of help in identifying clinical markers of cancer and therapy resistance.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| CSC | = | Cancer Stem Cells |
| DCGR | = | DiGeorge Critical Region |
| EMT | = | Epithelial-Mesenchymal Transition |
| GCL | = | Glutamate-Cysteine-Ligase |
| GCLC | = | Catalytic Subunit of GCL |
| GCLM | = | Regulator Subunit of GCL |
| GLS | = | Glutaminase |
| GLUT | = | Glucose Transporter |
| GPx | = | Glutathione Peroxidase |
| GR | = | Glutathione Reductase |
| GSH | = | Glutathione |
| GSS | = | Glutathione Synthetase |
| GSSG | = | Oxidized GSH |
| GST | = | Glutathione-S-Transferase |
| HCC | = | Hepatocellular Carcinoma |
| HMGA | = | High Mobility Group AT-hook |
| HO-1 | = | Heme Oxygenase 1 |
| IGF | = | Insulin like Growth Factor |
| JAK | = | Janus Kinase |
| Keap1 | = | kelch-like ECH-associated protein 1 |
| lnsRNA | = | long non-coding RNA |
| MAPK | = | Mitogen-Activated Protein Kinase |
| miRNA | = | microRNA |
| Nrf2 | = | nuclear factor (erythroid-derived 2)-like 2 |
| NSCLC | = | Non-Small-Cell Lung Carcinoma |
| PPP | = | Pentose Phosphate Pathway |
| PTEN | = | Phosphatase and Tensin Homolog |
| ROS | = | Reactive Oxygen Species |
| SLC7A11 | = | Solute Carrier family seven membrane element |

SNALP = Stable Nucleic Acid Lipid Nanoparticles

STIM = Stromal Interaction Molecule

TCA = Tricarboxylic Acid Cycle

TS-miRNA = Tumor Suppressive-miRNA

γ-GT = γ-glutamil-transferase

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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