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Original Article

Docosahexaenoic Acid (DHA) Impairs Docetaxel-Induced Up-regulation of miR-30a-5p and miR-126-5p Tumor Suppressors in Gastric Cancer Cell Line

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Abstract

Objective: Owing to the synergistic effects of omega-3 fatty acids with chemotherapeutic agents in boosting response rates in gastric cancer (GC) patients, they became a promising addition to cancer therapy. Due to microRNAs (miRNAs) involvement in various cellular functions, their alterations in response to therapeutic interventions can offer insight into the efficacy of treatments. Our objective was to investigate docosahexaenoic acid (DHA) effects in conjunction with docetaxel on miR-30a-5p and miR-126-5p expressions in the MKN-45 cell line.

Materials and Methods: The CancerMIRNome database was used to investigate miR-30a-5p and miR-126-5p expression changes, as well as their relation to diagnosis and survival in GC patients. Then, MKN-45 cells were treated with docetaxel, DHA, and their combination. Later, RT-qPCR was performed to measure miR-30a-5p and miR-126-5p expression levels.

Results: It was discovered that miR-30a-5p and miR-126-5p expression were both decreased in GC patients and associated with GC diagnosis and survival, respectively. Following treatment with docetaxel and docetaxel-DHA, miR-30a-5p and miR-126-5p expression levels increased. Of course, the increase in miRNAs' expression observed in the combination form was not as strong as docetaxel alone. DHA alone decreased miR-30a-5p and miR-126-5p expressions.

Conclusion: miR-30a-5p and miR-126-5p have important roles in GC tumorigenesis, and response to docetaxel and DHA. Attenuating effects of DHA on miR-30a-5p and miR-126-5p expression levels appear to counteract the beneficial effects of docetaxel on these miRNAs. Therefore, even though there is evidence of the anti-cancer effects of DHA in GC, not all DHA effects are anti-cancer.

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1. INTRODUCTION

Cancer is currently one of the fundamental health problems of any society, with a significant number of new cases and deaths each year. GC is one of the most widespread and fatal cancers, particularly in countries with unhealthy diets. According to the last available statistics, GC is the 5th most prevalent cancer and the third deadliest one globally (1). Late detection in GC patients is a major problem regarding their treatment. The late onset of symptoms means most GC patients are in late and severe stages upon diagnosis, contributing to the high mortality rate. Several risk factors have been reported for GC, including diet, lifestyle, genetic talent, family history, infections, and medical conditions and treatments. While many improvements have been made in different approaches to treating GC patients, the 5-year survival rate for GC remains poor. Chemotherapy is now a widely used therapy option in GC, increasing life expectancy and preventing tumor recurrence in many patients. Despite the impressive therapeutic effects of conventional chemotherapy on a wide range of patients, using appropriate chemotherapy regimens that are most likely to provide optimal therapeutic outcomes remains a crucial goal for these patients (2).

Omega-3, as a member of polyunsaturated fatty acids (PUFAs), have potential anti-inflammatory, anti-cancer, and cancer-preventive effects (3). DHA (an omega-3 fatty acid) is principally found in fish and fish oils and has shown promising results in treating cancers like GC (4).

miRNAs are among those factors that have significant regulatory effects on various cellular activities. They are single-stranded, non-coding RNAs with an approximate length of 18-25 nucleotides. Their regulatory effects occur at the post-transcriptional level, causing target mRNAs to become unstable and their translation to be suppressed. In cellular dysfunctions that lead to pathological conditions and diseases, the expression pattern of miRNAs differs from the normal situation, as seen in tumor cells. miRNAs are divided into two groups: oncomiRs and tumor-suppressors. OncomiRs are a group whose expression increases in tumor cells and intensifies as cancer progresses while tumor suppressor miRNAs decline. Their importance is so great that they have been proposed as diagnostic and prognostic biomarkers and therapeutic targets in cancer (miRNA replacement therapy) (5). miRNAs' expression is also affected by the response to the chemotherapeutic agents, which means that variations in the expression of particular miRNAs can predict a possible response or resistance to these drugs. Several studies have found a relation between altered miRNA expression patterns and chemotherapeutic drug response in GC patients. Many participate in the carcinogenic process as oncomiRs and others as tumor-suppressors and promote tumor progression (6). miR-30a-5p was identified as a tumor-suppressor miRNA in GC. It has been shown that GC cells with reduced expression of miR-30a-5p have a high potential for proliferation, invasion, and metastasis (7). miR-126-5p is involved in pivotal cell activities and its expression level changes during tumorigenesis. It is linked to GC patients' tumor growth, invasion, angiogenesis, and clinicopathological characteristics (8, 9). Previous studies have shown the relation between miR-30a and miR-126-5p expressions and response to chemotherapy drugs, including docetaxel (10-12).

In this study, a bioinformatics assay was performed primarily to investigate these two miRNA expression changes in GC patients and evaluate their importance in patients' diagnosis and overall survival (OS). Then, to find whether DHA in combination with the anti-cancer drug docetaxel has synergistic effects on the expression levels of miR-30a-5p and miR-126-5p, we assessed their expression changes in the MKN-45 GC cell line after using DHA, docetaxel, and their combined form.

2. MATERIALS AND METHODS

2.1. Online database analysis

The CancerMIRNome database (http://bioinfo.jialab-ucr.org/CancerMIRNome/) was used to investigate the alteration in the expression level of miR-30a-5p and miR-126-5p in different types of human cancers, including stomach adenocarcinoma (STAD), their relation with GC patients' OS, and diagnostic potential.

2.2. Cell line and reagents

MKN-45 cell line was obtained from the National Cell Bank of Iran (NCBI, Tehran). Cells were cultured in RPMI-1640 medium (Gibco, USA) supplemented with 10% fetal bovine serum (Gibco, USA) and antibiotics (Gibco, USA) in the air-humidified incubator (Memmert, Germany) with 5% CO2 at 37 °C. DHA solution and docetaxel were purchased from Sigma (USA) and Sanofi-Aventis (France), respectively.

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2.3. Cells treatments, RNA isolation, and cDNA synthesis

Briefly, MKN-45 cells (4.5×10^3 cells per well) were seeded into 6-well plates and then were treated with 100 µM concentrations of DHA and docetaxel (IC50 was previously determined (13)). After 24 hours, RNA extraction was performed using the RiboExTM protocol (Gene All Biotechnology, South Korea). Next, isolated RNAs' quantity and quantity were validated using electrophoresis on an agarose gel and optical density measurements with a Nanodrop spectrophotometer (Thermo Scientific, USA). Transcription of miRNAs into cDNA was done by cDNA Synthesis Kit II (Exiqon, Vedbaek, Denmark), according to the manufacturer's instructions.

2.4. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

The SYBR Green PCR Master Mix (Yecta Tajhiz Azma, Iran) was used for RT-qPCR. miRNA's reaction was prepared via mixing five µl master mix, one µl primer for miR-30a-5p and miR-126-5p (LNA™ PCR primer set, Exiqon, Denmark) (**Table 1**), four µl cDNA, and one µl DEPC water. The expression level of U6 was considered the reference gene. Three replicates of the experiment were conducted.

Table 1. Primer sequences

Target	Sequence(s)
miR-30a-5p*	5′-UGUAAACAUCCUCGACUGGAAG-3′
miR-126-5p*	5′-UCGUACCGUGAGUAAUAAUGCG-3′
U6*	5'-GGG CAG GAA GAG GGCCTA T-3'

*The sequence for the target sequence.

MiR-30a-5p: MicroRNA-30a, MiR-126-5p: MicroRNA-126, *U6*: U6 small nuclear RNA

2.5. Statistical analysis

The data were shown as mean ± SD of the fold difference between DHA-, docetaxel -, and Doce+DHA-treated and control cells. We analyzed the collected data using the Graph-Pad Prism software (version 6.0, USA) in conjunction with a student's t-test. *p*-value <0.05 was considered to be statistically significant.

3. RESULTS

3.1. Alteration in miR-30a-5p and miR-126-5p expressions and their relation with OS and diagnosis in STAD cases

Based on the findings obtained via the CancerMIRNome database, the expression levels of miR-30a-5p (p-value<0.0001) and miR-126-5p (p-value=0.12) were decreased in STAD cases compared to normal samples (**Fig 1**).

Kaplan-Meier (KM) plot analysis revealed that only miR-126-5p has a statistically significant relation with STADs' OS (p-value=0.012) (Fig 2C). While STAD cases with high miR-30a-5p expression showed a high survival probability, there was no statistically significant relation between miR-30a-5p and OS (**Fig. 2A**). Additionally, ROC (receiver operating characteristic) curve analysis showed that only miR-30a-5p has the potential to be used as a diagnostic biomarker in GC (Area under curve (AUC) = 0.82) (**Fig. 2B**).

3.2. DHA, docetaxel, and Doce+DHA treatments altered the expression level of miR-30a-5p

As shown in **Fig. 3**, RT-qPCR analysis showed that docetaxel increased miR-30a-5p expression in MKN-45 cells (p-value<0.0001 and +1.65 fold). However, DHA reduced its expression (p-value = 0.0089 and -0.53 fold). Also, their combination form, Doce+DHA, increased miR-30a-5p expression (p-value < 0.0001 and +1.21 fold).

3.3. DHA, docetaxel, and Doce+DHA treatments altered the expression level of miR-126-5p

The expression level of miR-126-5p (**Fig. 4**) increased following the treatment with docetaxel and Doce+DHA (*p*-value=0.0015 and +1.92 fold, *p*-value=0.0008 and +1.48 fold, respectively). However, DHA decreased its expression (*p*-value<0.0001 and -0.53 fold). All fold changes and *p*-values are mentioned in **Table 2**.

4. DISCUSSION

Even though the molecular mechanisms of omega-3 fatty acids are not yet fully understood, supplementing tumor cell membranes with these fatty acids alters the properties of the cell membrane, which in turn affects the signaling pathways involved in tumorigenesis (14). Although some studies have illustrated the advantages of taking omega-3 alone or in conjunction with chemotherapeutic agents,

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Table 2. Obtained fold changes and p-values

Target	Parameter	Docetaxel	DHA	Doce+DHA
miR-30a-5p	Fold change	+1.65	-0.53	+1.21
	p-value	<0.0001	0.0089	<0.0001
miR-126-5p	Fold change	+1.92	-0.53	+1.48
	p-value	0.0015	<0.0001	0.0008

miR-30a-5p: microRNA-30a-5p, miR-126-5p: microRNA-126-5p, Doce: docetaxel , DHA: docosahexaenoic acid

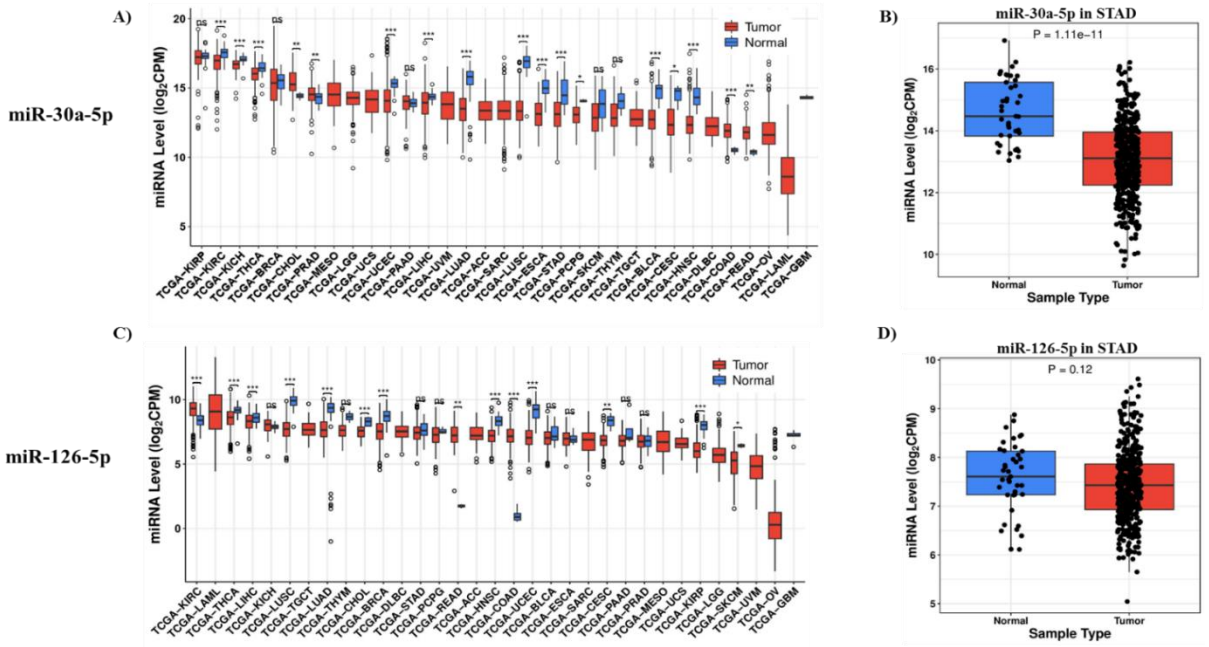

Figure. 1. The altered expression level of miR-30a-5p and miR-126-5p in STAD patients. Using online databases, CancerMIRNome, miR-30a-5p and miR-126-5p altered expression among different human cancers were investigated (A-C). Both miR-30a-5p (p<0.0001) and miR-126-5p (p=0.12) expressions showed decreased expression in STAD cases (B-D). *MiR-30a-5p: MicroRNA-30a-5p, MiR-126-5p: MicroRNA-126-5p, STAD: stomach adenocarcinoma*

there are inconclusive results, especially regarding GC (15-18). By using docetaxel, GC patients could live longer. However, there is a limit to how widely this drug can be used due to its side effects (19). Based on the good results reported for DHA, it could be a helpful therapy option when combined with docetaxel (20-23). miRNAs, as essential regulators of gene expression, undergo expression changes in response to anti-cancer agents, affecting various vital cell pathways. Initially, our analysis with the CancerMIRNome database confirmed reduced expression of miR-30a-5p and miR-126-5p in STAD samples. In addition, miR-30a-5p demonstrated diagnostic potential, and miR-126-5p was found to be associated with OS. We also showed that while using docetaxel alone increased miR-30a-5p and miR-126-5p expression levels, DHA decreased both. Furthermore, using docetaxel and DHA together increased miRNAs expression level, which was lower than docetaxel alone. Hence, it seems that DHA has no positive effect on the expression level of these two tumor-suppressor miRNAs in MKN-45 GC cells and reduces docetaxel's positive effect.

Downregulation of miR-30a-5p has previously been shown in GC. It contributes to the invasion and metastasis process in GC cell lines by targeting vimentin (24). Moreover, miR-30a-5p expression was related to GC patient survival (25). According to the study by Yu et al. (26), miR-30 was downregulated in GC tissues and showed an inverse relation with tumor progression and metastasis. Several studies have shown the link between miR-30a-5p and chemotherapy resistance and sensitivity; for example,

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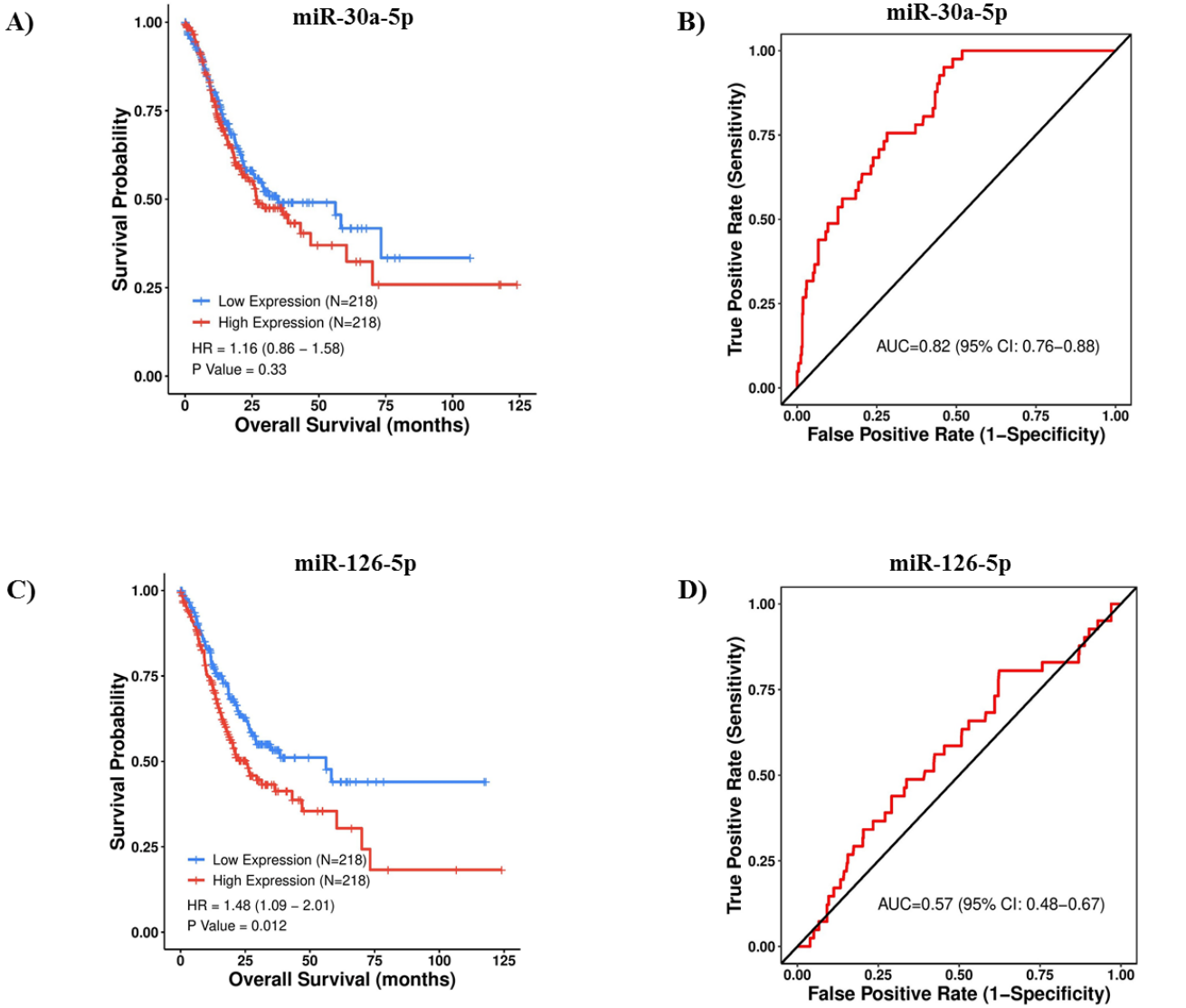

Figure 2. The correlation between the expression level of miR-30a-5p and miR-126-5p with STAD patients` OS and their diagnostic value. CancerMIRNome online databases showed that while miR-30a-5p expression has no relation with STAD patients' OS (p=0.33) (A), miR-126-5p has a statistically significant relation (p=0.012) (C). ROC-curve analysis of miR-30a-5p and miR-126-5p in STAD cases. MiR-30a-5p: MicroRNA-30a-5p, MiR-126-5p: MicroRNA-126-5p, STAD: stomach adenocarcinoma, OS: overall survival, ROC: receiver operating characteristic

it was introduced as a chemosensitivity-associated miRNA in GC. Du et al. (27) showed an association between miR-30a-5p and resistance toward cisplatin in SGC7901 GC cells. In another similar study, Wang et al. (28) showed that miR-30a-5p increased the cisplatin sensitivity of GC cells. They also showed that cisplatin-sensitive patients have a higher expression level of miR-30a-5p than the resistant group. As a result of these studies, miR-30a-5p has been shown to play a crucial role in GC progression and in the response to chemotherapy drugs. It has been shown that fatty acid consumption changes miR-30a-5p expression level. Chartoumpekis and his colleagues (29) reported that feeding mice with a high-fat diet (HFD) for five months downregulated miR-30a-5p in white adipose tissue. Previously, Elieh Ali Komi et al. (30) showed that while MDA-MB-231 breast cancer cells treatment of with paclitaxel, DHA, and LA alone increased miR-30a-5p expression, all combination forms decreased it. In line with the previous studies, we confirmed the decreased miR-30a-5p expression in STAD patients compared to normal samples, along with high diagnostic value and involvement in response to docetaxel and DHA. Furthermore, we found

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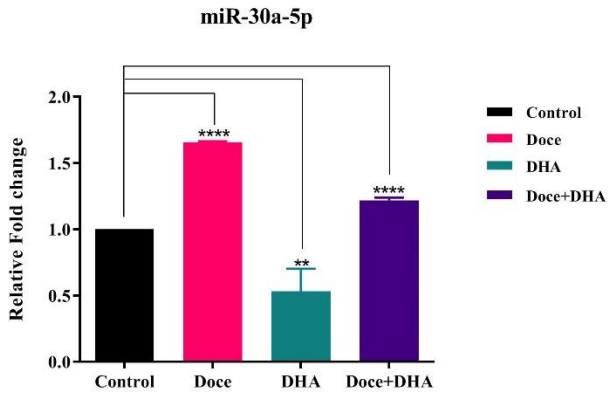

Figure 3. The altered expression level of miR-30a-5p following treatment of MKN-45 cells with Docetaxel and DHA. The cells were treated with DHA, Docetaxel, and their combination. After 24 h, the expression levels of miR-30a-5p in the treated and untreated (control) cells were determined with quantitative real-time PCR. * P-value <0.05, ** P-value <0.01, **** P-value <0.0001. *MiR-30a-5p: MicroRNA-30a, Doce: Docetaxel, Docetaxel, DHA: Docosahexaenoic acid*

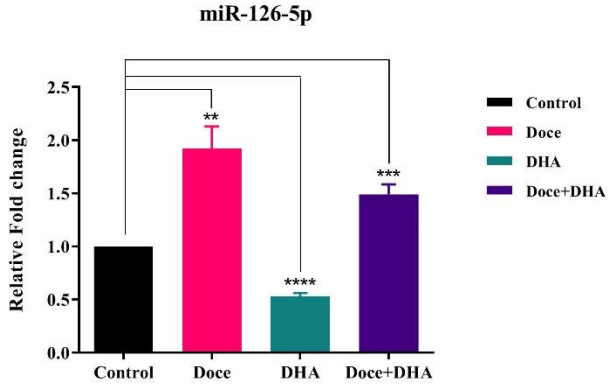

Figure 4. The altered expression level of miR-126-5p following treatment of MKN-45 cells with Docetaxel and DHA. The cells were treated with DHA, Docetaxel, and their combination. After 24 h, the expression levels of miR-126-5p in the treated and untreated (control) cells were determined with quantitative real-time PCR. * P-value <0.05, ** P-value <0.01, **** P-value <0.0001. *MiR-126-5p: MicroRNA-126, Doce: Docetaxel, Docetaxel, DHA: Docosahexaenoic acid*

that docetaxel increased miR-30a-5p expression in MKN-45 cells, which is related to the promising result of docetaxel treatment. However, DHA had the opposite effect on the miR-30a-5p expression level. It even reduced the positive impact of the docetaxel regarding increasing miR-30a-5p expression. Therefore, it seems that in addition to the positive effects of DHA, it also has adverse effects in some cases, including miR-30a-5p expression changes.

miR-126-5p is downregulated in digestive system cancers (DSCs), including GC, and acts as a tumor-suppressor miRNA. It targets oncogenes involved in metastasis, angiogenesis, and the epithelial-to-mesenchymal transition (EMT) process in tumor cells (8). Feng et al. (31) showed a lower expression level of miR-126-5p in GC cell lines, including MKN-45, and its association with tumor progression. By inducing miR-126-5p expression levels in SGC-7901 cells, the migration, invasion, and cell cycle arrest were suppressed. Moreover, induced expression of miR-126-5p increased tumorigenicity and metastasis in vivo. Several studies have revealed that miR-126-5p may affect angiogenesis by affecting angiogenesis-related genes (32). Wang et al. (33) discovered the tumor-suppressor role of miR-126-5p in GC and showed that miR-126-5p inhibits GC proliferation. They assessed miR-126-5p expression in GC tissues with different stages and cell lines, including MKN-45, and confirmed the decreased expression level of miR-126-5p. Moreover, they suggested miR-126-5p as a diagnostic biomarker and potential target for GC treatment. Many studies have found a link between downregulated miR-126-5p expression level and resistance to conventional chemotherapeutic drugs in various cancers, including GC. Wang et al. (34) showed low expression of miR-126-5p in vincristine (VCR) and Adriamycin (ADR) resistance cell lines. Concerning docetaxel and miR-126-5p, docetaxel-resistant breast cancer cells showed a significantly lower expression level of miR-126-5p than sensitive cells (10). Sarabi and colleagues (35) revealed that only DHA affected the promoter methylation status and miR-126-5p expression following treatment of colorectal cancer cell lines with PUFAs, including eicosapentaenoic acid (EPA), linoleic acid (LA), and DHA. They showed that while the expression level of miR-126-5p increased considerably by DHA in HCT116 and Caco2 cell lines, the increase was insignificant in HT29/219, LS10, and SW742 cell lines. In another study, DHA treatment along with paclitaxel significantly decreased miR-126-5p expression both alone and in combination forms in the MDA-MB-231 breast cancer cell line (30). So, it is evident that miR-126-5p has a role in response to docetaxel and DHA in different cancers. In line with the previous studies, our investigations first confirmed the suppressory role of miR-126-5p in STAD patients with its correlation with their OS, which means the importance of miR-126-5p expression in SKCM patients and also its involvement in response to docetaxel and DHA therapies. Additionally, increased miR-126-5p expression in MKN-45 cells after treatment with docetaxel indicates that docetaxel treatment has favorable effects.

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However, DHA has unexpected effects regarding miR-126-5p expression level and even reduces the positive effect of docetaxel. Indeed, DHA weakened the positive effect of docetaxel on miR-126-5p rather than strengthening it, and this was the same pattern observed regarding miR-30a-5p.

5. CONCLUSION

Consumption of omega-3 fatty acids during chemotherapy has raised hopes that chemotherapy side effects can be reduced. However, comprehensive studies on the molecular mechanisms and intracellular effects of DHA are the missing piece of the puzzle. As a piece of this enormous puzzle, our study showed that DHA affects the expression level of miR-30a-5p and miR-126-5p. Unexpectedly, when DHA is used as a supplementary agent along with docetaxel, it attenuates its effects in MKN-45 GC cells. Therefore, it seems that adding DHA as a supplementary agent does not improve docetaxel's effects in all directions, but it also has side effects. Of course, it could not be claimed that these decreasing effects of DHA are ultimately attenuating docetaxel effects because the downstream pathways and their several targets are so broad that they need to be studied on a large scale. Further research is required in order to confirm its effects, especially at the molecular level.

Acknowledgment

None

Conflict of interest

The authors declare no conflict of interest.

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Ethical considerations

All tests here are in vitro, and there is no intervention in the living organism. The materials used are completely harmless and do not have any clinical side effects.

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