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EXPERIMENTAL STUDY

Inhibition of voltage-gated potassium channels affect expressions of miR-126 and miR-126* in breast cancer cell lines

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ABSTRACT
AIM: We aimed to determine the possible correlation between voltage-gated potassium channels and micro RNAs in breast cancer and metastatic breast cancer cells.
METHOD: Kv1.3 and Kv10.1 channels were inhibited by specific siRNAs using a lipofectamine-based transfection in MCF-7 and MDA-MB-231 cells. After transfection, total RNA was isolated, and then miR-126 and miR-126* expressions were observed using RT-PCR.
RESULTS: There was a negative correlation between Kv channels and miRNAs according to the characteristics of the breast cancer cells. The inhibition was observed not only in Kv1.3 but also in Kv10.1 in MCF-7 cells, and miR-126 and miR-126* expressions were downregulated compared to the control group ($p < 0.001$). The inhibition of these channels in MDA-MB-231 cells caused an upregulation of miR-126 and miR-126* expressions ($p < 0.001$).
CONCLUSION: The miR-126 and miR-126* expressions differed according to benign and malign breast cancer cell lines. Furthermore, we found that miR-126/126* may interact with Kv1.3 and Kv10.1 voltage-gated potassium channels. Our study suggests and indicates the relationship between Kv channels and miRNAs in breast cancer cells *(Tab. 1, Fig. 2, Ref. 51)*. Text in PDF *www.elis.sk.*
KEY WORDS: breast cancer, Kv1.3, Kv10.1, miR-126, miR-126*.

Introduction

Breast cancer has the highest prevalence among cancer types in women. There are various endogenous and exogenous reasons for the development of breast cancer. Hormonal regulation, gene mutations, and epigenetic mechanisms are some examples of endogenous reasons of breast cancer. In gene regulation, the role of voltage-gated potassium channels (VGPC; Kv) are important for preserving homeostasis. Several studies showed that a change or an increase in the channel function is associated with the formation of tumors (1). Previous studies indicate that the Kv channels play a critical role in the proliferation of tumor cells. Therefore, potassium channels may have a role in identifying various biomarkers in various cancers (2–4).

Voltage-gated potassium channels of the Kv1.3 type are integral membrane proteins, which are activated ("open") upon a change in the cell membrane potential, thus enabling a passive flux of potassium ions across the cell membrane (5, 6). Kv1.3 describes a mammalian shaker-related voltage-gated potassium channel encoded by the KCNA3 gene (6). Studies performed in the last decade provide evidence that Kv1.3 channels are expressed not only in the plasma membrane, but also in the inner mitochondrial membrane (6–8). The suppression of Kv1.3 channel expression by application of Kv1.3 targeting siRNA significantly reduces the ability of both normal and leukemic T lymphocytes to undergo apoptosis induced by staurosporine (6, 9). The upregulation of channel activity that occurs via the caspase 8-dependent pathway generates a sustained outward current that was required to promote the efflux of potassium ions and cell shrinkage, which are hallmarks of cell apoptosis (6, 10). Kv10.1, a member of the EAG family, is mostly studied in cancer. Indeed, Kv10.1 has been reported to have oncogenic properties (11, 12). It is observed that Kv10.1 is overexpressed in primary solid tumors including breast cancer (11, 13). In MCF-7 cells, Kv10.1 regulates the cell cycle progression, where it allows the entry of the non-invasive BC cells in G1 phase by hyperpolarizing the membrane potential and increasing the cytosolic Ca concentration (14, 15). Furthermore, Kv10.1 also regulates migration in the MDA-MB-231 cells via Ca entry through the Orai1 channel (16).

Micro RNAs (miRNAs) negatively regulate gene expression by binding to the 3′ untranslated region (3'-UTR) of target mRNAs, thus altering mRNA abundance at the post-transcriptional level, as well as allowing for transcriptional modification (17). It has been shown that non-coding regulatory RNAs play a particular role in

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Tab. 1. Forward and reverse sequences of the primers used in RT-PCR.

PRIMER	FORWARD SEQUENCE	REVERSE SEQUENCE
miR-126	3'-GTCCGCTCGTACCGTGAGTAATA-'5	3'-CCAGTCTCAGGGTCCGAGGTATTC-'5
miR-126*	3'-CGCGCTCATTATTACTTTTGGTA–5'	3'-CCAGTCTCAGGGTCCGAGGTATTC-'5
GAPDH	5'-CGAGGGGGGAGCCAAAAGGG-'3	3'-GAAACTGCGACCCCGACCGT-'5

formation and progression of cancer (18). MiR-126, which usually refers to the 3′ part of the transcript, (also called miR-126-3p), is located within the seventh intron of EGFL7, which resides in human chromosome 9 (17, 19-21). MiR-126*, referring to the 5′ part of the transcript (also called miR-126-5p), is the analogous strand to miR-126, which binds to the main miR-126 transcript in the stem loop structure of the pre-miRNA (17, 20). MiR-126 is one of the many miRNAs that have important roles in cellular biology, including cancer biology. Schmidt and colleagues reviewed the two main functions of miR-126, namely angiogenesis and inflammation, and briefly stated that miR-126 may play critical roles in various cancers (17, 20). MiR-126 is markedly downregulated in human breast cancer tissues. The increase in expression of miR-126 was reported to lead to suppression of the breast cancer cell invasion (22). MiR-126 was shown to be one of several miRNAs with varying expressions in samples of breast carcinoma obtained from 30 patients and ranging from malignant to benign (17, 23). Hafez et al suggested that the low expression of miR-126 in 40 breast cancer samples was associated with metastasis and other clinical and pathological features of breast cancer (17, 24). There are more studies concerning the miR-126 function in carcinogenesis. The results of these studies showed that miR-126 maintains its role as a suppressor of metastasis that could reduce the metastatic rate and size of breast carcinoma (17). One of our previous research results indicated that miR-126 can affect the characteristics of breast cancer cell lines, and showed the impact of miR-126 on genetics of breast cancer cells, especially on metastatic breast cancer cells (25). We aimed to determine the relationship between Kv channels and miRNAs in breast cancer. We also focused on the important impact and difference of cell characterization (malign or being characterization of cancer cells) on the same gene expressions. Moreover, we wanted to point to the future use of Kv channels (as a biomarker or/and in therapy) in breast cancer from the micro RNA perspective.

Materials and methods

Cell culture and transfection

MCF-7 and MDA-MB-231 breast cancer cell lines (ATCC, Washington D.C., USA) were maintained in Medical Biology Laboratory of Eskisehir Osmangazi University. phenol red free DMEM high glucose (DMEM; Gibco, UK) with 10 % fetal bovine serum (FBS; Gibco, UK) and 1 % Penicillin/Streptomycin (FBS; Gibco, UK) were used to culture MCF-7 and MDA-MB-231. The cells were maintained in a humidified atmosphere with 5 % CO_2 at 37 °C.

Before transfection, MCF-7 and MDA-MB-231 cells were incubated in 6-well plates (Greiner, Germany) to make sure the cells grow to 80 % confluence. After confluency, MCF-7 and MDA-MB-231 cells were transfected with Kv1.3- and Kv10.1-specific siRNAs by using lipofectamine-based transfection method (Thermo Scientific, USA). By using serum-free medium (Gibco, UK), Kv1.3- and Kv10.1-specific siRNAs and lipofectamine-based transfection reagent were incubated for 10 minutes separately. After incubation, mediums were gently mixed. The appropriate antibiotic-free complete medium (Gibco, UK) was added to the solution which was then transferred to the flasks. According to our study design, we have three comparable groups. The control group was non-transfected; Kv1.3 group was Kv1.3-transfected and Kv 10.1 group was Kv10.1-transfected.

Total RNA isolation and real-time polymerase chain reaction (RT-PCR)

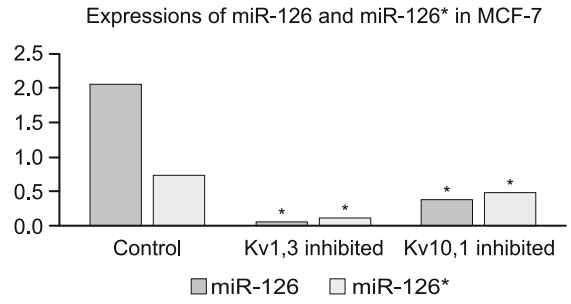
Total RNA was isolated from cells using Paris Total RNA Isolation Kit (Carlsbad, USA) as per the instructions of the manufacturer. Primer sets for amplification of miR–126, miR-126* and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were designed and supplied by Alpha DNA (MontReal, Quebec). The primer sequences used in RT-PCR are shown in Table 1. RT-PCR was performed in Stratagene MxPro3000 (Stratagene, UK). GAPDH was used as an internal control, and the expressions of miRNA and mRNA were normalized to the expression of GAPDH. Gene expression changes were quantified using the delta-delta CT method ($2^{-\Delta\Delta Ct}$). Fold changes of expressions were calculated through relative quantification.

Statistical analysis

The normal distribution of continuous variables was enabled using the Kolmogorov–Smirnov suitability test. The comparisons between groups of normally distributed variables were evaluated using one-way variance analysis (ANOVA). The Tukey HSD test was used for multiple comparisons. Multiple comparisons of these groups were evaluated using the Dunn test, while normally distributed miRNA values were compared using the Student-t test. All analyses were carried out using the IBM SPSS Statistics 21.0 software package. The obtained data were indicated as mean ± standard deviation (sd). Values with $p < 0.05$ were considered statistically significant. Statistical evaluations were performed by Eskisehir Osmangazi University, Department of Biostatistics.

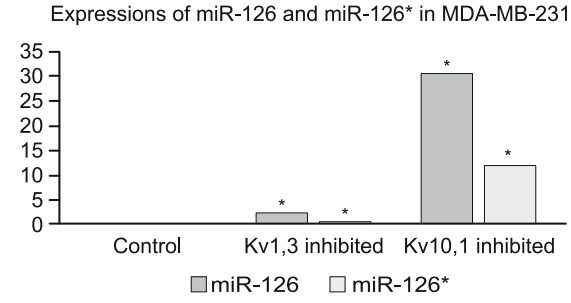
Results

According to the data obtained in the current study, miR-126 (0.06) and miR-126* (0.126) expressions decreased in the Kv1.3-inhibited adherent breast cancer cell line, MCF-7 cells, compared to the control (2.06/0.74) (Tukey HSD test; $p < 0.001$) (Fig. 1). The expression patterns in the Kv10.1-inhibited MCF-7 cells were very similar to those observed in the Kv1.3-inhibited MCF-7 cells.



	Control	Kv1,3 inhibited	Kv10,1 inhibited
miR-126	2.06	0.06	0.40
miR-126*	0.74	0.13	0.48

Fig. 1. Micro RNA-126 (miR-126) and its complementary miR-126* expressions in MCF-7 cells after inhibition of Kv1.3 and Kv10.1 voltage-gated potassium channels. Kv1.3 and Kv10.1 inhibition by small interfering RNA (siRNA) transfection caused a decrease in miR-126 and its complementary miR-126* in MCF-7 cells. All data obtained were evaluated compared to the control group ($p < 0.001$).



	Control	Kv1,3 inhibited	Kv10,1 inhibited
miR-126	0.05	2.43	30.48
miR-126*	0.01	0.53	12.04

Fig. 2. Micro RNA-126 (miR-126) and its complementary miR-126* expressions in MDA-MB-231 cells after inhibition of Kv1.3 and Kv10.1 voltage-gated potassium channels. While Kv1.3 and Kv10.1 channels were inhibited in MDA-MB-231 cells, both miR-126 and its complementary miR-126* expressions were upregulated. All data obtained were evaluated compared to the control group ($p < 0.001$).

The expressions of miR-126 (0.40) and miR-126* (0.48) were downregulated in Kv10.1-inhibited MCF-7 cells compared to the control group (2.06/ 0.74) (Tukey HSD test; $p < 0.001$) (Fig. 1).

There were some changes in the expressions of miRNAs according to various cancers or different types of the same cancers. We observed different expressions of miRNAs in different types of breast cancer cells, while Kv1.3 and Kv10.1 VGPCs were inhibited. The expressions of both miR-126 (2.43) and miR-126* (0.53) increased in the invasive breast cancer cell line, MDA-MB-231 cells, compared to the control group (0.05/0.01) while the Kv1.3 channel was inhibited (Fig. 2) (Tukey HSD test; $p < 0.001$). Moreover, the inhibition of the Kv10.1 channel in MDA-MB-231 cells caused an upregulation in miR-126 (30.48) and miR-126* (12.04) expressions compared to the control group (0.05/0.01) (Fig. 2) (Tukey HSD test; $p < 0.001$).

Discussion

According to the data we obtained, the inhibition of Kv1.3 and Kv10.1 channels caused breast cancer cells to change miR-126 and its complementary miR-126* expressions. Furthermore, we determined that these changes depended on the characteristics of breast cancer cells. MCF-7 cells are benign, adherent and estrogen-dependent breast cancer cells whereas MDA-MB-231 cells are malign, invasive and estrogen-independent breast cancer cells. Our results showed that in MCF-7 cells, the inhibition of Kv1.3and Kv10.1 caused a downregulation of miR-126 and miR-126* expressions, which are related to metastasis in breast cancer cells. According to our previous study, the inhibition of Kv1.3 and Kv10.1 caused MCF-7 cells to decrease oxidative stress, which also depends on the invasiveness of breast cancer cells (26). From the data obtained from both studies, it appears that the inhibition of these channels might cause a positive change in the aggressiveness of MCF-7 cells. In addition, Kv1.3 and Kv10.1 inhibition caused MDA-MB-231 cells to upregulate miR-126 and miR-126* expressions. In our previous study, we observed that oxidative stress increased when metastasis-related Kv10.1 channel is inhibited. However, Kv1.3 inhibition affects the oxidative stress level positively in MDA-MB-231 cells (26). In brief, the results from both of our studies show that although Kv10.1 inhibition might be increased in MDA-MB-231 cells, Kv.1.3 inhibition might affect the malignity of MDA-MB-231 cells. Our previous studies also showed that the inhibition of voltage-gated potassium channels by selective and non-selective inhibitors disrupted the antioxidant/oxidant balance and increased oxidative stress in breast cancer cells (27). Moreover, miR-126 and miR-126* expressions are generally upregulated in breast cancer cells using these selective and non-selective voltage-gated potassium channel inhibitors (28). Our data obtained in the current study also support our previous findings and we think that there is an interaction between voltage-gated potassium channels and micro RNAs according to the characteristics of breast cancer cells.

While determining the relationship between Kv channels and miRNAs, there was no previous study in accordance with this relationship. Because of this situation, it is hard for us to cite any previous study possibly related to our study. Furthermore, both Kv channels and miR-126 have an important role in breast cancer and its metastasis. Therefore, it is quite difficult to suggest a novel hypothesis with limited assays. In our study, we observed the cause of the inhibition of Kv channels on miR-126 and miR-126* expressions. Our research in this paper only discriminates the relationship according to their gene expression. From this perspective, our results on this relationship can become the preliminary data for this research area.

Voltage-gated potassium (Kv) channels are known to play a pivotal role in the progression of various cancer types and are considered as new targets for designing anti-cancer therapy (29). Numerous studies have reported deregulated Kv channel expres-

sion in human cancer. For example, overexpression of Kv10.1 is found in 70% of cancer types (13, 29) and high expression of Kv1.3 is detected in a number of malignancies, including breast, colon and prostate cancers (29–31). Several studies have demonstrated the altered expression of Kv1.3 in some cancer specimens in comparison with normal tissue (6, 31–33). An increased expression of Kv1.3 channels was observed in cases of breast, colon, smooth muscle (leiomyosarcoma), skeletal muscle (alveolar rhabdomyosarcoma), and lymph node cancers (2, 31) as well as in mature neoplastic B cells in chronic lymphocytic leukemia (B-CLL) (6, 34). A significantly increased expression of protein in the channels was shown in cancer cells when compared to normal tissue (2, 6). The knock-down of Kv1.3 channels by applying the siRNA technique eliminated the sensitivity of Jurkat T cells to apoptosis induced by the inhibitors of Kv1.3 channels (6, 35). Markedly reduced expression of Kv1.3 channels at both mRNA and protein levels was detected in a case of breast adenocarcinoma, and there was an inverse correlation between the channels' expression and tumor grade (6, 36).

There are several studies investigating the relationship between microRNAs and potassium channels in cancer. The potassium channel KIR4.1 (KCNJ10) plays an important role in regulating the cell membrane potential. Lin et al demonstrated that inhibition of miR-205 disrupted the wound-healing process in human corneal epithelial cells by targeting KIR4.1 (KCNJ10). MiR-205 provided wound healing by inhibiting potassium channels KCNJ10 (37). Li et al reported that methylglyoxal (MGO), which is highly produced with constant hyperglycemia, contributed to diabetic vascular problems. Their functional assays indicated that K(ATP) currents were impaired by miR-9a-3p stimulated with MGO treatment. Their research showed that MGO exposure induced the expression of miR-9a-3p. miR-9a-3p subsequently reduced SUR2B mRNA, compromising the function of the K(ATP) channel in vascular smooth muscles (38). In another research, miR-190 appeared to be a positive organizer of $Ca^{(2+)}$ influx and played a critical role in hypoxic pulmonary vascular constriction. Li et al revealed that miR-190 had a positive effect on the process of the KCNQ5 potassium channel (39). The purpose of the research was to show the effects of miR-1 on the atrial effective refractory period (AERP) in a right atrial tachypacing model and explain the potential mechanisms. Suppressing miR-1 induced the expression of KCNE1 and KCNH2. Consequently, it was indicated that KCNE1 and KCNB2 were potential targets of miR-1 (40). Another study showed that miR-194 regulated the activity of the ROMK channel (ATP-dependent potassium channel, Kir1.1) by modulating ITSN1 (intersectin 1) expression. The authors suggested that miR-194 might regulate the activity of the ROMK channel (ATP-dependent potassium channel, Kir1.1) by modulating ITSN1 (intersectin1) expression in HEK293T human embryonic kidney cells (41).

Some microRNAs have been seen to play a role in the formation of cancer and development mechanism. Quinidine is known to have anti-proliferative and pro-apoptotic effects, and Ru et al demonstrated that voltage-gated potassium channel blocker quinidine regulates some miRNAs expression (42). Meng et al (2012) previously reported that IC50 values were reduced in cells treated with miR-155 inhibitor together with taxol compared to a control group treated with taxol alone. Furthermore, the miR-155 inhibitor reduced apoptosis in glioblastoma multiforme cells (43). In another study, it was found that when hEAG in the voltage-gated potassium channel was inhibited, the expression of miR-34, a tumor suppressor, was increased. Lin et al demonstrated that the level of miR-34 was related to hEAG expression in the SHSY5Y human neuroblastoma cell line (44). Kv1.1 is a voltage-gated potassium channel. Sosanya et al provided evidence of a novel mechanism for mTORC1 kinase-dependent translational regulation of mRNA of Kv1.1. They found out that while mTORC1 was active, miR-129 suppressed Kv1.1 mRNA translation (45). HERG1, human ether-à-go-go-related potassium channel, plays a key role in cellular processes. A further study identified hERG1 as the target of miR-96, which is downregulated in pancreatic cancer cell lines and tissues. The researchers suggested that miR-96 acted as a tumor suppressor in cancer. Thus, miRNA may serve as a therapeutic target for pancreatic cancer (46). In the research conducted by Wu et al., human osteosarcoma was used as the model and miR-34a was shown to be downregulated in osteosarcoma tissues. The authors also found that overexpression of miR-34a led to reduced ether à go-go 1 (hEAG1) potassium channel expression in osteosarcoma cells. Their results suggest that miR-34a could inhibit osteosarcoma cell growth due to the downregulation of EAG1 expression (47). Other researchers determined that miR-296-3p was downregulated in U251AR glioblastoma cells by finding out that EAG1 was over-expressed. Bai et al reported that EAG1 expressions correlated with miR-296-3p in tissue specimens. Their findings suggest that miR-296-3p may play a role of MDR in glioblastoma (48). A similar study in glioma revealed that miR-133b contributes to arsenic-induced apoptosis in U251 cell line by targeting the hERG (Kv11.1, KCNH2) channel. Targeting the miR-133b/hERG pathway may be a new strategy for chemotherapy of malignant gliomas (49). KCNMA1 is a member of calcium-activated large-conductance potassium channel belonging to the subfamily of M alpha. A previous study showed that the overexpression of miR-31 or the loss of KCNMA1 led to increased cisplatin resistance in ovarian cancer cells (50).

In their research, Mazar et al demonstrated that down-regulation of miR-211 and the corresponding upregulation of its target transcript KCNMA1 were important molecular events for melanoma development and/or progression (51). In our previous study, we suggested that miR-126/126* might interact with voltage-gated potassium channels. We observed that the inhibition of K channels using potassium channel blockers resulted in an increase in miR-126/126* expression in non-invasive breast cancer cells (MCF-7) but not in invasive breast cancer cells (MDA-MB-231) (28).

To our knowledge, this is the first study to investigate the effect of inhibition of voltage-gated potassium channels on microRNA-126 expression in cancer cells. Therefore, we think that our study will greatly contribute to future studies on voltage-gated potassium channels and miRNAs. Moreover, these data may be a source for considering these properties in gene therapies for

breast cancer types. Further studies are needed to obtain detailed information on the relationship between voltage-gated potassium channels and miRNAs in cancer.

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