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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 24(4): 361-370 (2024)
DOI: 10.31901/24566322.2024/24.04.872

# Role of the miR-93-5p/SRGN Axis in Proliferation, Invasion and Apoptosis of HER2-positive Breast Cancer Cells

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**KEYWORDS** Breast Cancer. Biological Function. Expression. Malignant Transformation. miRNA

**ABSTRACT** This research intended to investigate the biological function of serglycin (SRGN) in breast cancer (BC) with positive human epidermal growth factor receptor 2 (HER2). The expressions of SRGN and micro-ribonucleic acid (miR)-93-5p in HER2-positive BC tissues as well as the target binding sites between them were analysed using bioinformatics software. The propagation, movement, infiltration and apoptosis of these cells were determined by corresponding assays. SRGN had low expression in the cells of HER2-positive BC. Increasing the SRGN expression attenuated the proliferation and metastasis and induced HER2-positive BC cell apoptosis. Molecular assays revealed that miR-93-5p negatively modulated SRGN expression. The overexpressed miR-93-5p in HER2-positive breast cancer cells reversed the role of SRGN overexpression in repressing tumour cells from the aspect of malignant phenotype. To sum up, the miR-93-5p/SRGN axis exerts a pro-metastatic effect on HER2-positive breast cancer, indicating that suppressing this axis may be a new strategy for treatment.

## INTRODUCTION

Breast cancer (BC) has been recognized as the leading reason for cancer-related death of women (Katsura et al. 2022). Regardless of great treatment development for BC in recent decades, the annual global mortality rate remains high (Hashemi et al. 2020). The high-degree genetic heterogeneity of BC may lead to the prevalence and persistence of the disease (Zhang et al. 2017; Baslan et al. 2020). Being a proto-oncogene (Ahn et al. 2020), human epidermal growth factor receptor 2 (HER2) is highly expressed in 15-20 percent of patients with breast cancer and thus in the case of HER2-positive BC, contributes to the high relapse rate and unsatisfactory prognosis (Zheng et al. 2019). Hence, the molecular mechanism of HER2-positive breast cancer needs to be investigated for guiding individualised treatment.

As a glycoprotein with low molecular weight, serglycin (SRGN) has distribution in cells, which can be combined with the extracellular matrix after being secreted from cells (Zhu et al. 2021). SRGN not only has crucial functions in preserving and secreting various cytokines, proteases and chemokines, but also participates in numerous pathophysiological processes (Kolset and Pejler 2011; Scully et al. 2012; Manou et al. 2020). According to reports, SRGN presents abnormal expressions in a number of carcinomas, and its high expression has relations to nasopharyngeal carcinoma (Li et al. 2011; Wang et al. 2022) besides non-small cell lung cancer (Guo et al. 2017; Guo et al. 2020) regarding the progression and metastasis. Additionally, SRGN is a crucial downstream target of HIF-1α, which facilitates the progression and metastasis of colorectal cancer by modulating the transcription of SRGN (Xu et al. 2018; Kim et al. 2021). As denoted by Lv et al. (2021), a high expression of SRGN was detected from osteosarcoma, while down-regulating SRGN expression affected osteosarcoma cells by suppressing their movement together with invasion. Therefore, SRGN is closely associated with tumour metastasis.

In this study on HER2-positive BC, the SRGN was detected for its expression, and the influence of SRGN overexpression on the malignant progression of tumour cells was assessed.

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### Objectives

The present research aims to explore SRGN for its biological role in HER2-positive BC, and to provide a possible method for treating this type of cancer.

## MATERIAL AND METHODS

### Bioinformatics Analysis

The Cancer Genome Atlas database was selected to download the messenger ribonucleic acid (mRNA) (normal: 113 and tumour: 145) and micro-ribonucleic acid (miRNA) expression (normal: 104 and tumour: 144) levels of HER2-positive breast cancer to analyse the differences. The target mRNA was identified by literature retrieval, and the upstream miRNA was predicted by the mirDIP and miRWalk databases. GSEA software was applied for the pathway enrichment analysis of target genes.

### Cell Culture

ATCC (USA) supplied HER2-positive BC cells (SK-BR-3 and BT-47) together with human breast epithelial cells (MCF10A). 293T cells were supplied by BNCC (China). The culture of the above cell lines was accomplished at $37^0$C using an incubator containing 5 percent $CO_2$ and Dulbecco's Modified Eagle medium (DMEM) (Invitrogen, USA) supplemented with 10 percent foetal bovine serum (FBS) (Invitrogen, USA).

### Cell Transfection

The plasmids mimic-negative control (NC), oe-SRGN, oe-NC and miR-93-5p-mimic (miR-mimic) bought from Ribobio (China) were subjected to transfection into cells by means of the Lipofectamine™ 2000 kit (Thermo Fisher Scientific, USA).

### Quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR)

TRIzol reagent (Invitrogen, USA) was applied to obtain total RNA from cells for reverse transcription to cDNA by virtue of PrimeScript RT Master Mix (Takara, Japan). The CFX96 real-time PCR detection system (Bio-Rad Laboratories, USA) was employed to perform qRT-PCR *via* miScript SYBR Green PCR Kit (Qiagen, Germany) to determine the gene expression level. With the standardised endogenous controls set as U6 and GAPDH, the $^{2-\Delta\Delta Ct}$ method was adopted to measure the relative expression levels of different molecules. Table 1 presents the sequences of primers.

### Cell Counting Kit-8 (CCK-8) Assay

A 96-well plate was utilized for cell inoculation, with CCK-8 solution (Kumamoto, Japan) supplemented in a volume of 10 μL at 0, 24, 48, 72, and 96 hours, respectively. The 450 nm wavelength was examined to acquire the absorbance following 2 hours of incubation.

### Colony Formation Assay

The cells were seeded in a 6-well plate subsequent to trypsin (0.25 %) digestion. Next, the FBS (10 %)-containing DMEM was used for 2 weeks of room-temperature cell culture under 5 percent $CO_2$. The medium was removed when there were visible colonies. Afterward, 4 percent paraformaldehyde fixation, 10-minute crystal violet (0.1 %) staining, and PBS rinsing were carried out on the colonies. Lastly, the cell colonies were counted.

**Table 1: Sequences of primers used for qRT-PCR**

| *Primer* | *Sequence (5'-3')* |
|---|---|
| miR-93-5p forward | ACACTCCAGCTGGGCAAAGTGCTGTTCGTGC |
| miR-93-5p reverse | CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGCTACCTGC |
| U6 forward | CTCGCTTCGGCAGCACATATACT |
| U6 reverse | CGCTTCACGAATTTGCGTGT |
| SRGN forward | CAGGTATTCAAGGTCCCATTTCA |
| SRGN reverse | GGACTACTCTGGATCAGGCTT |
| GAPDH forward | GATGCTGGCGCTGAGTACG |
| GAPDH reverse | GCTAAGCAGTTGGTGGTGC |

### Dual-luciferase Reporter Assay

After the construction of pmirGLO-SRGN-3'-untranslated region (UTR)-WT plus pmirGLO-SRGN-3'-UTR-MUT luciferase reporter vectors (Promega, USA), a 96-well plate was used for inoculation of 293T cells ($2\times10^5$ cells/well), followed by co-transfection of SRGN-WT/SRGN-MUT plasmids or miR-mimic/mimic NC into cells. After 48 hours of incubation, the dual-luciferase reporter assay system (Promega, USA) was employed to determine the luciferase activity.

### RNA Binding Protein Immunoprecipitation (RIP) Assay

The RIP kit (Millipore, USA) was applied to test the binding of miR-93-5p to SRGN. The supernatant of SK-BR-3 cells was abandoned following washing in pre-cooled PBS. Subsequently, the cells underwent 5 minutes of lysis in an ice bath with lysate (P0013B, Beyotime) added in an equivalent volume and 10 minutes of 4°C centrifugation (14,000 rpm), with the supernatant harvested. The following experimental operations were selected. Firstly, magnetic beads (50 μL) from different coprecipitation reaction systems underwent suspension in RIP wash buffer (100 μL) after being cleaned, which were incubated with the antibody (5 μg). Later, the magnetic base was utilized to harvest the magnetic bead protein complex from the sample. Ago2 (Invitrogen, USA), the antibody used in RIP, was added for 30 minutes of room-temperature blending. With the negative control determined as IgG (Invitrogen, USA), RNA was extracted from the sample digested with proteinase K for later assays.

### Transwell Assay

For cell migration assay, a serum-free medium was used for suspension of BT-474 or SK-BR-3 cells ($1\times10^5$/well), which were seeded in the Transwell system (Corning, USA) from the upper chamber. The lower chamber was supplemented with the FBS (10 percent) containing DMEM. Subsequently, the cells invading the lower chamber were subjected to crystal violet (Sigma, Japan) staining after 24-hour culture. Regarding cell invasion assay, matrix gel (BD Biosciences, USA) was applied in a volume of 50 μL to cover the upper chamber of the Transwell system. The remaining operations were identical to those in cell migration assay. Finally, the assay results were observed and analysed under a microscope.

### Statistical Analysis

SPSS 22.0 software and GraphPad 5.0 software were utilized to accomplish statistical analysis and plotting, respectively. The format of mean ± standard deviation ($\bar{x} \pm s$) was adopted to describe measurement data, and the between-group comparison of means was conducted *via* the *t*-test. $P<0.05$ signified a difference with statistical significance.

## RESULTS

### Down-regulation of SRGN in HER2-positive BC

SRGN functions as an essential participant in the cancer metastasis (including breast cancer) (Zhang et al. 2020). Therefore, SRGN may exert a similar effect on the progression of HER2-positive breast cancer. Based on bioinformatics database analysis, HER2-positive BC tissues, in comparison with adjacent tissues, had significantly down-regulated SRGN expression (Fig. 1A). As revealed by qRT-PCR results, SRGN expression levels were significantly lower in HER2-positive BC cells (SK-BR-3 and BT-474) than in the human breast epithelial cells (MCF10A) (Fig. 1B). According to the pathway enrichment analysis, SRGN was involved in the cell apoptosis pathway. The above findings indicated that SRGN may work as a tumour suppressor gene during HER2-positive BC progression.

### Effect of SRGN on Malignant Behaviours of HER2-positive BC Cells

Oe-NC and oe-SRGN groups were established to assign SK-BR-3 and BT-474 cells, for the purpose of exploring the biological function of SRGN in HER2-positive BC advancement. qRT-PCR was conducted on the cells first to measure the transfection efficiency. In comparison to the control group, overexpressing SRGN significantly increased the expression of SRGN in SK-BR-3

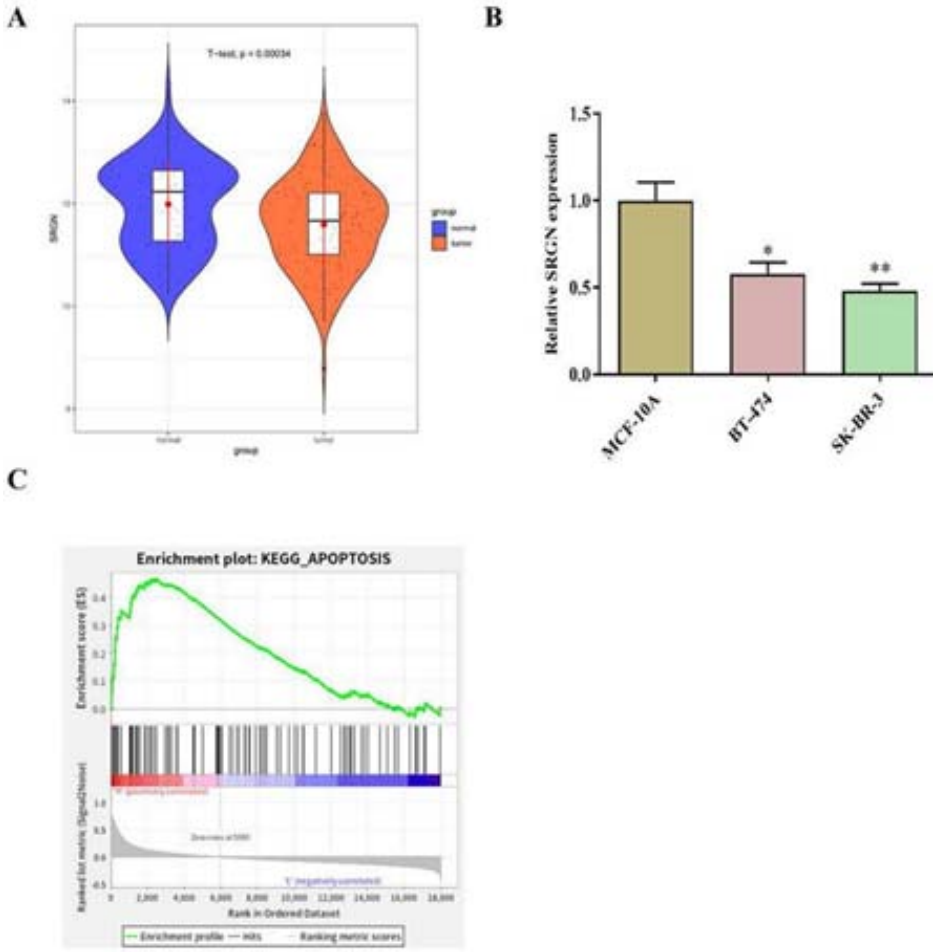


**Fig. 1. SRGN is significantly down-regulated in HER2-positive BC. A: SRGN expression in HER2-positive BC tissues. B: SRGN expression in cell lines. C: GSEA pathway enrichment analysis**
****P<0.01**

and BT-474 cells (Fig. 2A). According to CCK-8 and colony formation assays, SRGN overexpression significantly suppressed SK-BR-3 and BT-474 cells in terms of their activity and proliferation (Fig. 2B and 2C). Additionally, the up-regulation of SRGN expression significantly attenuated the migrating and invasive abilities of SK-BR-3 plus BT-474 cells (Fig. 2D and 2E). Moreover, the apoptosis rates of SK-BR-3 and BT-474 cells were evidently raised subsequent to the up-regulation of SRGN expression (Fig. 2F). These findings indicated that SRGN functioned as an inhibitor for HER2-positive BC cells concerning their multiplication and metastasis.

## MiR-93-5p Targetedly Regulated SRGN Expression

To further clarify the molecular mechanism of SRGN in influencing HER2-positive BC from the aspect of malignant progression, the relationship between mRNAs (predicted by mirDIP and miRWalk databases) and differentially up-

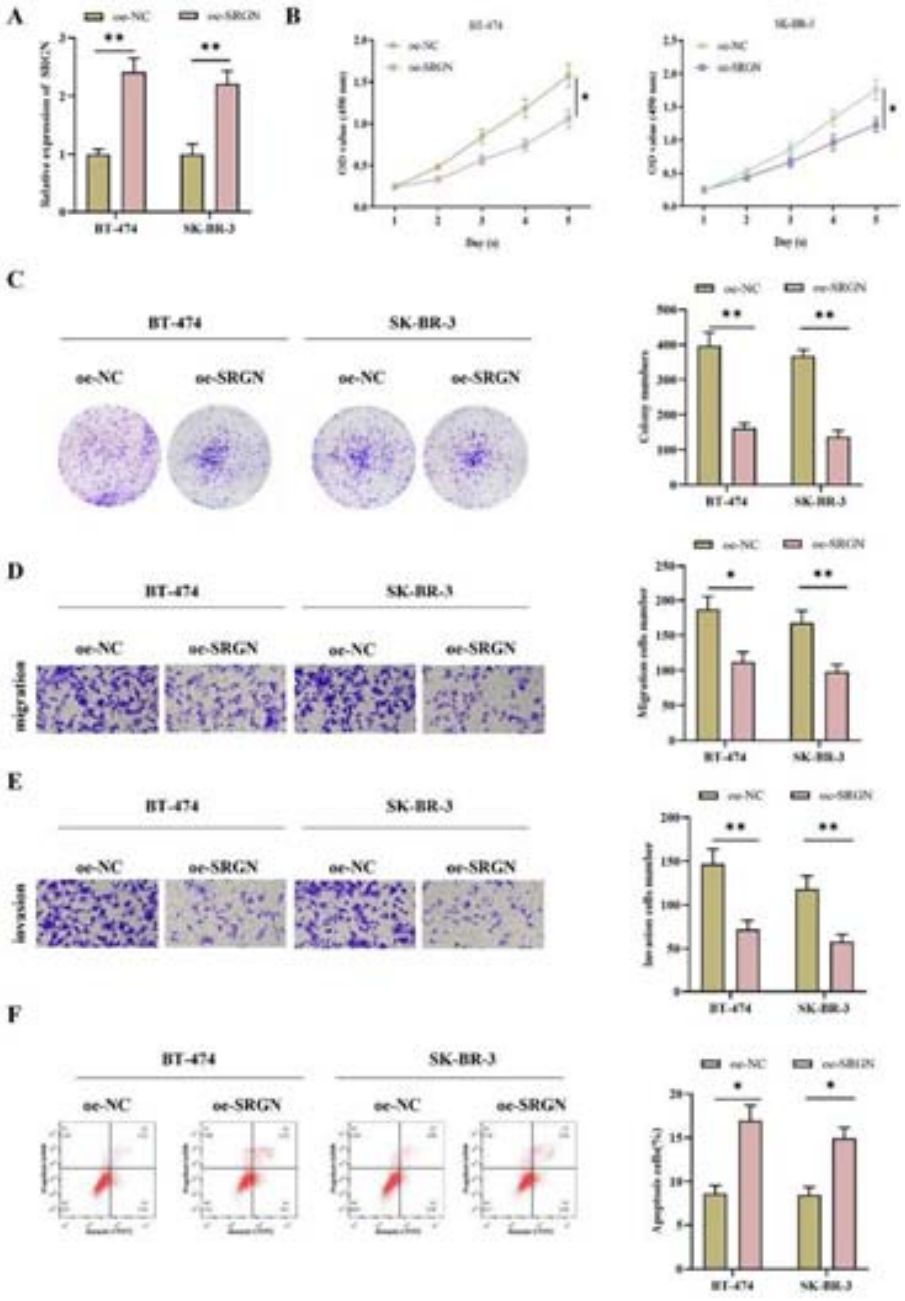


**Fig. 2. Role of SRGN in affecting malignant behaviors of HER2-positive BC cells. A: SRGN expression in cells. B: Analysis of cell viability. C: Analysis of cell proliferation. D-E: Cell migration and invasion analyses. F: Cell apoptosis rate analysis**
***P<0.05, and **P<0.01**

regulated miRNAs was identified through the analysis of bioinformatics database (Fig. 3A). Pearson analysis revealed a negative association of miR-93-5p with SRGN (Fig. 3B), and up-regulation of miR-93-5p expression was observed in HER2-positive breast cancer tissues (Fig. 3C). Moreover, bioinformatics analysis was carried out to forecast the site for miR-93-5p to conjugate with SRGN (Fig. 3D). Next, *in vitro* cell experiments demonstrated significant up-regulation of SRGN expressions in SK-BR-3 and BT-474 cells (HER2-positive BC cells) compared to those in the human breast epithelial cells (MCF10A) (Fig. 3E). The results of the dual-luciferase reporter assay illustrated that the 293T cells exhibited reduced SRGN-WT luciferase activity due to the up-regulation of miR-93-5p expression (Fig. 3F). Moreover, RIP assay results also validated that SRGN was the direct target of miR-93-5p (Fig. 3G). Finally, miR-mimic and mimic-NC were constructed to treat SK-BR-3 cells. The miR-mimic group displayed a significantly lowered mRNA expression level of SRGN by contrast to the control group (Fig. 3H). Collectively, SRGN was the direct target of miR-93-5p.

### Role of miR-93-5p in Affecting Malignant Behaviours of HER2-positive BC Cells by Targeting SRGN

For the purpose of exploring how the miR-93-5p/SRGN axis impacts on HER2-positive BC, mimic NC + oe-NC, miR-mimic + oe-NC, and miR-mimic + oe-SRGN groups were created to allocate SK-BR-3 cells. Overexpressing miR-93-5p significantly down-regulated SRGN expression in SK-BR-3 contrasted with that in the control group, while further overexpressing SRGN reversed this effect, according to the qRT-PCR results (Fig. 4A). The results of CCK-8 assay manifested that the viability of SK-BR-3 cells was prominently facilitated by miR-93-5p overexpression, whereas the simultaneous overexpression of miR-93-5p and SRGN restored the viability to the level of the control group (Fig. 4B). Furthermore, it was uncovered by colony formation assay together with Transwell assay that overexpressing miR-93-5p remarkably enhanced the proliferative, migrating and invasive abilities of SK-BR-3 cells, which can be reversed by further overexpressing SRGN (Fig. 4C-4E). Finally, the results of cell apoptosis assay denoted that the SK-BR-3 cell apoptosis rate was notably lowered by miR-93-5p overexpression but restored to the level of the control group by the simultaneous overexpression of miR-93-5p and SRGN (Fig. 4F). Taken together, miR-93-5p can induce the propagation and metastasis of HER2-positive BC cells by modulating SRGN expression.

## DISCUSSION

BC emerges as the most frequently occurring malignancy in females around the globe (Cao et al. 2021). HER2-positive BC takes a proportion of nearly 15-20 percent to the total cases, and positive HER2 indicates a poor prognosis (Bray et al. 2018). Despite several studies revealing the mechanism of HER2-positive breast cancer progression (Swain et al. 2023), the detailed mechanism remains inconclusive. The results of this study revealed that SRGN may function as a tumour suppressor gene during HER2-positive BC advancement, and the miR-93-5p/SRGN axis probably exerts a regulatory effect.

As a small-molecule glycoprotein related to cancer metastasis, SRGN is packaged into secretory granules and vesicles in platelets, megakaryocytes and all bone marrow cells (Schick 2010; Tanaka et al. 2022). Previous studies have discovered the expression of SRGN in endothelial cells (Ma et al. 2020), hematopoietic cells (Hwang et al. 2021) and embryonic stem cells (Zhang et al. 2020). Moreover, overexpression of SRGN is associated with the malignant progression and invasive biological behaviour of tumours (He et al. 2014; Purushothaman and Toole 2014; Hosoya et al. 2022). In the case of giant cell tumour of bone, for example, the knockout of SRGN at a high expression level can suppress the generation of osteoclasts and promote tumour growth (He et al. 2021). Hamilton *et al*. (2015) found that SRGN deletion facilitates the primary tumour growth and angiogenesis in the spontaneous insulinoma formation model of RIP1-Tag2 mice due to tumour heterogeneity. Likewise, this study indicated that SRGN was significantly lowly expressed in HER2-positive BC cells. After SRGN expression was up-regulated, HER2-positive breast cancer cells mani-

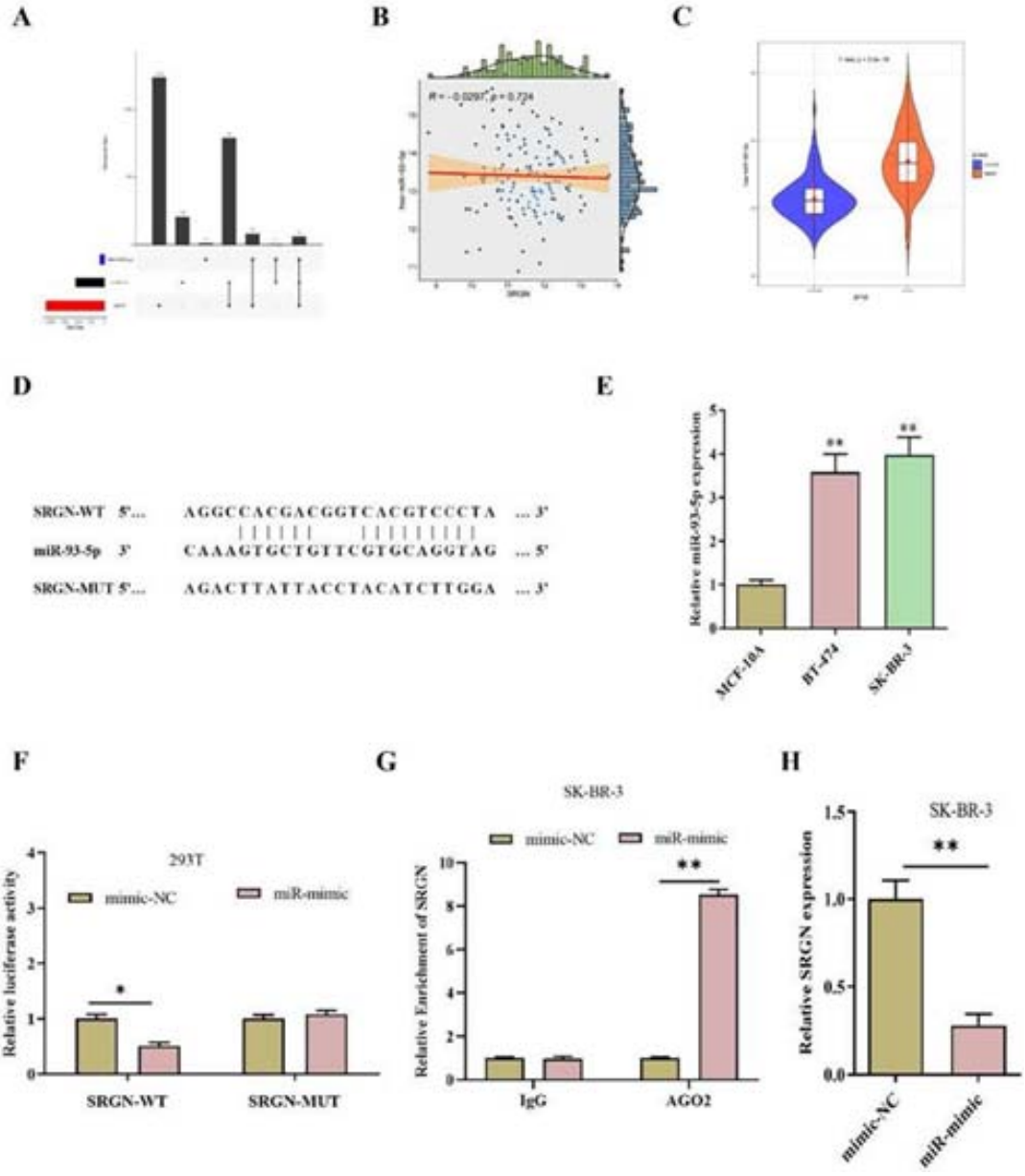


**Fig. 3. MiR-93-5p targetedly regulated SRGN expression. A: Upset plot of mRNAs together with differentially up-regulated miRNAs through bioinformatics database analysis. Figure B: Correlation graph. C: MiR-93-5p expression in HER2-positive BC tissues. D: Targeted binding sites of miR-93-5p and SRGN. E: MiR-93-5p expression in HER2-positive BC cell lines. F-G: Validation of the functional relation of miR-93-5p to SRGN. H: Expressions of SRGN in HER2-positive breast cancer cell lines *P<0.05, and **P<0.01**

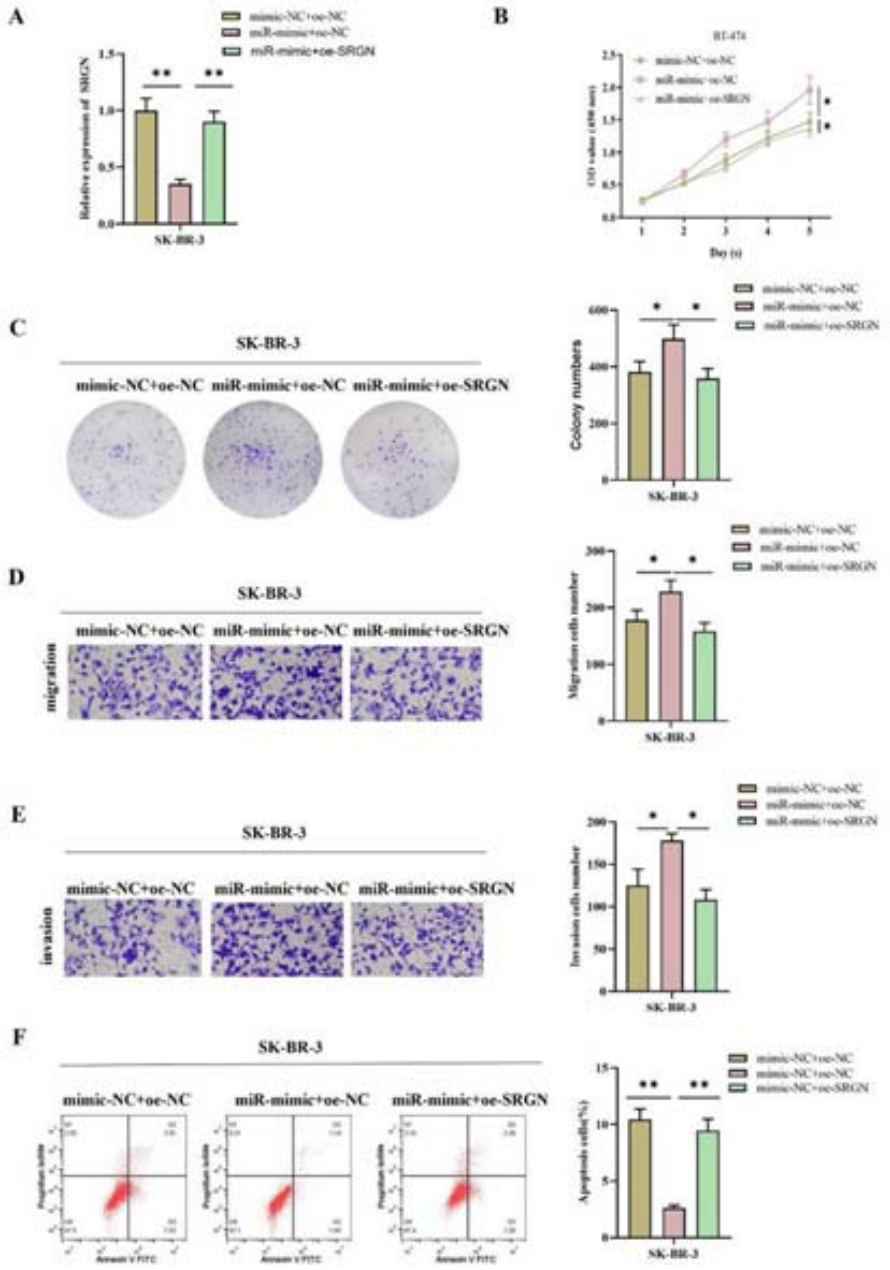


**Fig. 4. Cellular miR-93-5p expression. B: Analysis of cell activity. C: Cell proliferation analysis. D-E: Cell migration and invasion analyses. F: Cell apoptosis rate analysis**
***P<0.05, and **P<0.01**

fested inhibited proliferation and metastasis. Taken together, SRGN has the potential to become a novel molecular target for inhibiting HER2-positive BC metastasis.

The exact mechanism by which SRGN inhibits the metastasis of HER2-positive BC was explored in the present research. The upstream regulatory molecule of SRGN, namely miR-93-5p, was identified to target the negative regulation of SRGN expression. As a class of non-coding RNAs encoded by endogenous genes (Ali et al. 2020), miRNAs exert carcinogenic or oncogenic effects by influencing the malignant biological behaviours (for example proliferation, apoptosis, radiation resistance, chemical resistance, and metastasis) (Li et al. 2013; Kampen et al. 2017; Srivastava et al. 2019). For instance, it has been demonstrated that miR-93-5p is a pivotal miRNA for regulating cancer progression. It is a tumour suppressor gene in ovarian carcinoma (Chen et al. 2022), colorectal carcinoma (Chen et al. 2020), and glioma (Wu et al. 2019). MiR-93-5p can conjugate with the 3'-UTR of CCND2 to negatively regulate CCND2 expression, thus suppressing ovarian carcinoma cells from propagation and movement. The researchers herein found high miR-93-5p expression in HER2-positive BC cells, consistent with findings of previous research on non-small cell lung cancer (Yang et al. 2018), esophageal carcinoma (Liu et al. 2018), as well as hepatocarcinoma (Li et al. 2021). Interestingly, overexpressing SRGN reversed the mechanism of miR-93-5p overexpression in affecting HER2-positive BC cell phenotype. Hence, restraining miR-93-5p expression or elevating SRGN expression may be conducive to suppressing the growth plus survival of HER2-positive BC cells.

## CONCLUSION

In conclusion, SRGN functions as a tumour suppressor for HER2-positive BC breast cancer *in vitro* from the aspect of cell migration and invasion. Additionally, SRGN is a direct downstream target of miR-93-5p, as well as a vital player in mediating the pro-tumorigenesis effect of miR-93-5p in HER2-positive breast cancer cells.

## RECOMMENDATIONS

Aiming at the miR-93-5p/SRGN axis can serve as a new promising therapeutic method for HER2-positive breast cancer.

## ABBREVIATIONS

DMEM: Dulbecco's modified Eagle medium
FBS: foetal bovine serum
HER2: human epidermal growth factor receptor 2
miRNA: micro-ribonucleic acid
mRNA: messenger ribonucleic acid
NC: negative control
qRT-PCR: quantitative reverse transcription-polymerase chain reaction
RIP: RNA binding protein immunoprecipitation
SRGN: serglycin
UTR: untranslated region

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**Paper received for publication in December, 2022**
**Paper accepted for publication in January, 2024**