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PROFILING BREAST CANCER CELLS TO ELUCIDATE SOME EPIGENETIC FACTOR TO CONTROL THE DISEASE

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Abstract

Background: Breast cancer (BC), the disease's incidenceis elevating global wide with major elevation in riskyneoplasiain women with young ages. Among all cancers, women are facing, breast cancer is the most disease that cause fear for women as it affects their self-esteem and confidence.

Aims: current study aimed at establishing a prediction model for breast cancer that is based on epigenetic and genetics readings.

Material and methods: In this study, We used MCF-7 breast cancer cells were able to recognise the role of around 95 different types of microRNAs**:**The results of study are show that about 95 mi-RNAs- profiled, 6 mi-RNAs were found to be up-regulated, and 26 mi-RNAs were found to be down-regulated. The prediction of disease has been leading to recognising the special relation, the miRNAs which are up-regulated is with common illness including cancer.

Conclusion: To reach early breast cancer diagnosis, the up-regulated miRNAs which were 6 can be used as a biomarkers. Also, has-miR-23b-3p was overexpressed and is found in a high expression profile so it is considered a potential biomarkers. Notwithstanding, more investigations and further studies are needed to support these findings.

Keywords: BC - miRNA- MCF 7- Profiling-Epi-genticbiomarker potential- Immunology

Cancer is a general term that encompasses a wide range of illnesses.that can affect various organs in the body. Cells have a natural tendency to divide and die in a predictable pattern [1,2]. On the other hand, Cancer cells have the ability to divide uncontrollably indefinitely [3,4].There are over 200 distinct cancer kinds [5-7]. With 8.8 million fatalities each year, The second leading cause of death on the planet is cancer. [8].

Breast cancer, on the other hand, is the most common invasive malignant tumour in women and the second leading cause of cancer death in women after lung cancer, with 1.5 million new cases diagnosed each year and over 500,000 cases diagnosed worldwide [9-11]. It is a heterogeneous disease that involves changes in both mRNA and micro-RNA (miRNA) expression profiles and affects a wide range of neoplasms.[12-16]

Early detection using proven methodsand regular monitoring of the patient's therapeutic reactionare required to properly monitor BC [17,18]. However, due to the decrease of authorisedbiomarkers with high sensitivityfor early detection or diagnosis of the illness, these tasks are unexpectedly difficult to accomplish [17,18].The use of microRNA in the early detection of breast cancerand other malignancies has recently received a lot of attention [19-22]. Given the simplicity with which miRNA may be isolated, characterised, and quantified, it could be used as a trustworthy biomarker. MiRNA could be employed as prognostic or predictive biomarkers in addition to early diagnosis of BC [22-24].In BC miRnome, extensive study has revealed remarkable discoveries, Some of these have already been acceptedfor use inTherapeutic settings[23] MiRNA research is currently ongoing, and it shows great potential in terms of finding new Therapeutic targets and biomarkers.[25-27].MRNAS are a type of short noncoding RNA molecules with

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a single strandthat have evolved to be evolutionary preservedand are coded by about 1% of the gens in many animals. These are included in the post-transcriptional control of genome term [28-30].Some miRNAs are well-known for acting as major negative regulators in a variety of biological processes that contribute to breast cancer [31]. MicroRNA expression abnormalities linked to cancer give a good starting point for investigating itsIn cancer, it serves a useful purpose [13,32,33].Unregulated miRNAs discovered in before christmay help us better understand the tumour microenvironment, prompting more research into their function in cancer growth and metastasis [34-36].

In the last decade, several types of studies have focused on establishing the relationship between distinct miRNA and BC bymiRnome profiling in cancer cells and patients[20,37-39]. This aids in elucidating the functional role and molecular mechanisms of down/up-regulated microRNAs in the formation and progression of BC, which is required for miRNA-based therapy to progress. [13,15,24]

accessoriesand process

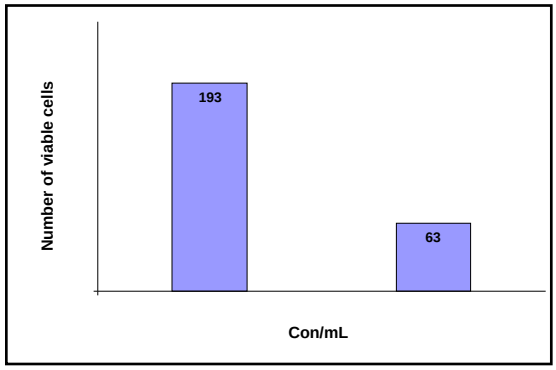
Cell Culture

MCF 7 (Breast Cancer) cell line provided from VACSERA (Holding Company for Biological Products and Vaccine), (Cairo- Egypt.). On a 12-well plate, cells were seeded at a density of 104 cells/cm2 and cultured in RPMI 1640 media .(supplemented with 10% FBS (Hyclone, Logan, UT) and 1% antibiotic mix at laboratory conditions (37°C and 5% CO2)

To control genomic drift due to instability, the MCF-7 cell line was involved in the study throughout the first 10 passages from the flask which was originally bought. Every three days, the RPMI-1640 was altered, and the cells were transfected when they reached 65 to 80 percent confluency.

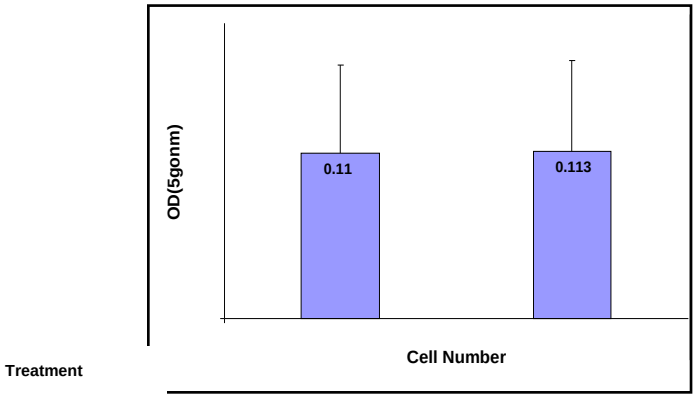
Trypan- blue staining

The incubation of cell was with trypan blue stain (Invitrogen- 15250-061) this can be done after procaine drug transfection. The cell which retained the dye dead and also which excluded the dye viablewere counted on achemo-cytometer slide under a type light microscope. The dilution of is done trypan blue dye of exclusion medium of acid by preparing a dilution 1:1 of cell suspension using 0.4%trypan blue solution.



MTT

The assessing of cell viability 3-(4&5-dimethylthiazolyl-2)- 2&5 diphenyltetrazine bromide assay (MTT). In about 96 well plate, each well was loaded 5x10 cells and cultured until confluence reaches to 65%. MTT was carried out directly after applying siRNA. Many wells are left in the aim of control. The control and treated wells were loaded with put in each .media which supplied with MTT solution. 20 µl of solution of MTT (5 mg/ml) was used in the experiment well including control wells. Then incubation of cells for 3 hours in a 5 % CO2 incubator. Then aspirated 50 µl media and then added 180 µl DMSO to each well. Then transferred the plate to a shaker water bath with 37°C which is ambient temperature at 250 rpm for 30 minutes to dilute the formazan crystals.



Total protein extraction

The RNeasy kit was used to extract total RNA from MCF-7 cells (Qiagen, Germany). DNase I (Boehringer-Mannheim, Mannheim, Germany) was used to treat RNA for 50 minutes before purification according to the kit's instructions. Spectrophotometry and ethidium bromide agarose gel electrophoresis were used to assess the quality and integrity of the RNA.

First-strand cDNA synthesis

In a 4.75 L volume, 200 ng poly RNA, 0.6 L semi-random primer, and ribonuclease-free water were added to a 0.2 mL PCR tube. In a hot-lid thermal cycler, the mixture was incubated for 3 minutes at 72°C, cooled for 2 minutes on ice, and then incubated for 10 minutes at 25°C. 5x in 2 u litresSMARTScribe buffer, 0.5 25 mM 5'SMART tag, 1 litre 10 mMdNTP mix, 0.25 litres 100 mM DTT, 0.5 litresRNaseOUT (Invitrogen), and 1 litreSMARTScribe Reverse Transcriptase (100 U) were produced and placed in the tube (Clontech). In a thermal block, the mixture was incubated for 90 minutes at 42°C, followed by 10 minutes at 68°C. In order to digest the RN, 1 litre of RNase H (Invitrogen) was added to the solution.

Double-stranded cDNA synthesis

11 litres of first-strand poly(A) cDNA, 74 litres of Milli-Q water, 10 litres of 10x PCR buffer, 2 litres of 10 mMdNTP mix, 1 litre of 25 mM 5' SMART PCR primer, and 2 litres of 50x Polymerase Mix (Clontech). A 100-L reaction mixture was incubated at 95°C for 1 minute, 68°C for 20 minutes, then 70°C for 10 minutes to extend the primers. Double-check your work till it's finished.

B.4. PCR array

The generated cDNA has been subjected to RTPCR against the specific primer (1ul for each primer) gene expression was calculated according to the threshold of the cycle all reaction volume was 25ul containing about (12.5) µl of SYRP Green Master Mix. Program of the thermal cycler was(95) c for (15) min, and fourteen cycles for (94) c for fivteen sec, (54) c for (30) sec. and (72) c for thirty sec. Internal control was achieved by utilising GAPDH

Analyzing data

The CT amount were collected and uploaded to Qiagen's online analysis tool [40], where data validation and 2-CT calculations for each miRNA were carried out.

Statistical analysis

IBM-SPSS-24 (IBM-SPSS- Inc. Chicago- IL) can be used for conducting of data analyses. ± SD is the expression of all values. Determining the significance of the different in a multiple comparison can be done using analysis of variance with t-test. P value differences were less 0.05.

Results

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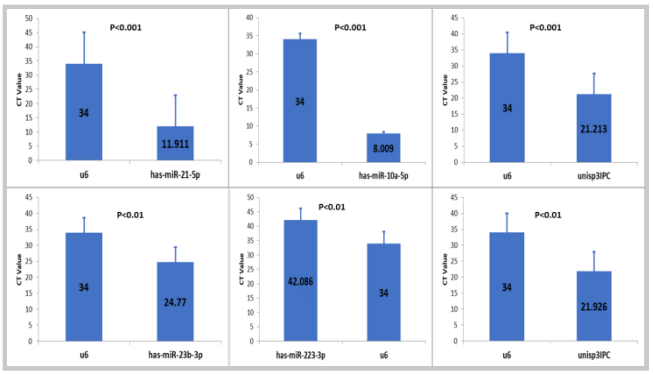
A. Up-regulated miRNA in Breast cancer

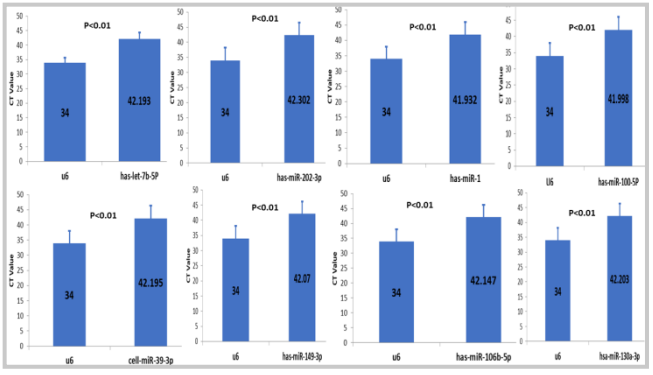
In this work, 95 miRNAs were identified in breast cancer cells (MCF-7). Six miRNAs, hsa-miR-21-5p, hsa-miR-10a-5p, has-miR-23b-3p, hsa-miR-223-3p, unisp-31pc, and unisp-3pc, were shown to be elevated in BC cells (Figure 1)



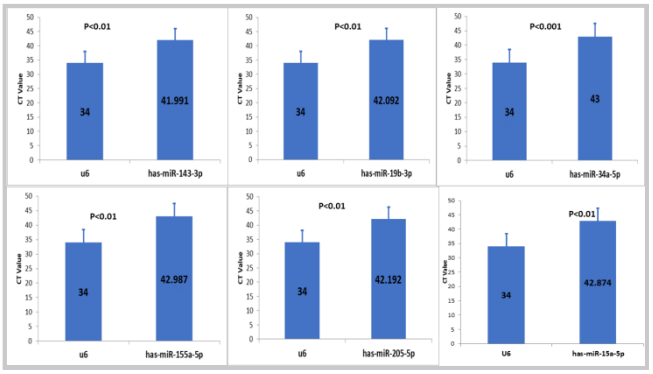
The considerable differences were estimated between all the studied mi-RNA ($p<0.001$) and U6 snRNA, with especially one exception for hsa-miR-106a-5p because the differences wasn't appear clearly at thep-value which is the same.

B. Down regulated miRNAs in BC

In this study, 95 miRNAs were profiled, with 26 miRNAs being down-regulated in breast cancer cells: "has let 7b 5p, miR 202 3p, miR 1, miR 100 5p, miR 39 5p, miR 139 3p, miR 106b 5p, and miR 130a 3p" (Figure 2)



Furthermore, the down-regulated gene "had miR 143 3p, miR 19b 3p, miR 34a 5p, miR 155a 5p, miR 205 5p, and miR 15a 5p," according to the study (Figure 3)



Furthermore, the miR 30c 5p, miR 30b 5p, miR 29b 5p, miR 29b 3p, miR 26b 5p, and miR27a 3p were all found to be down-regulated in breast cancer cells (Figure 4)

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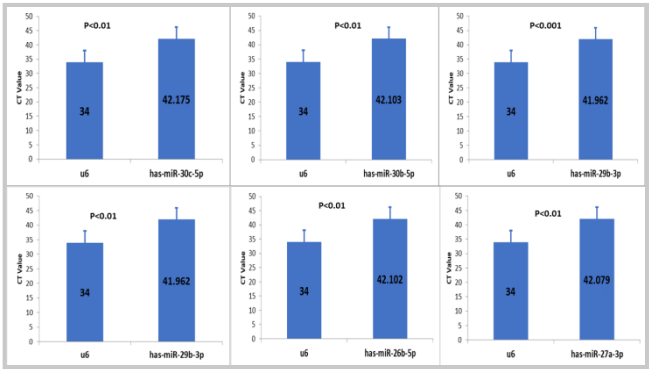
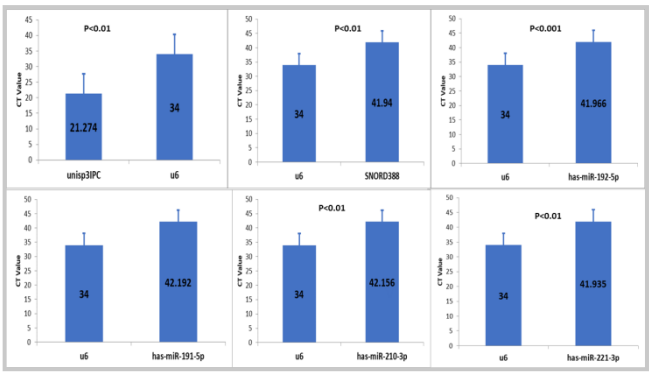


Similarly, BC cells showed down-regulation of miR 192 5p, miR 191 5p, miR 210 3p, miR 221 3p, unisp31 pc, and SNORD388 (Figure 5)



The signification of differences between U6 snRNA and the expression level of the target mi-RNA were ($p<0.01$ and 0.001). Several miRNAs exceptions were recorded; "hsa-let-7c-5p, hsa-let-7d-5p, has-miR-206, has-miR-25-3p, has-miR-196a-5p, has-miR-30b-5p, hsa-let-7g-5p, has-miR-18a-5p and hsa-214-3p" as the expression level differences wasn't clear and wasn't significant at the same p-value.

Discussion

In the current study, the profile of 95 miRNAs was presented in cells of BC (MCF 7) with the toentifying a biomarker. Some found to be down-regulated which were about 26 of these miRNAs, and some found to be up-regulated in cells of breast cancer about 6 in a comparison to U6 sn-RNA as it has an internal control inRT-PCR - depend on expression analysis.

A. Up-regulated miRNAs

The clear differences between U6 sn-RNA except (has- miR- 106a- 5p) and these miRNAs were revealed by statistical analysis where the obtaining of non-significant differences occur.**(Fig. 1).**Earlier obtaining of this profile as Minn, Lee [37] was an indication for the increasing of BC expression. It has been reported that in "hsa-miR-196a-5p" the levels of apoptosis is elevated resembling GC-2 cells treated, which mean that it is involved in cancer cells apoptotic machinery [38]. Both hsa-miR-21 and hsa-miR-17-5p were significant high in cell lines and tissues of breast cancer, where AIB1 gene down-regulate primarily via translational inhibition. Meanwhile,overexpression ofhsa-miRNA-17-5p promotesand control the proliferation of cells which induces growth of tumor [39,40].

The "has miR 195 5p" suppresses the proliferation &invasion & migration ofcarcinoma squamous cell Many miRNAs that have been discovered to be up-regulated "hsamiR 103a 3p has -miR-21-5p, and has miR 195 5p" should be employed as breast cancer diagnostic biomarkers. [40-42]. The up-regulation of "have miRNA-19a-3p" reduced cancer growth and metastasis in both the bladder and the breast by inducing macrophage polarisation through the

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expression of down-regulation of the "Fra-1" proto-oncogene in vivo [43], and in the oral cavity via targeting TRIM14 in vivo [44].

B. Down-regulated miRNAs

About 95 of the miRNAs investigated in this study were found to be down-regulated in breast cancer cells, with about 26 of them being shown to be down-regulated. It resulted in "hsa-mir-30c" enhancing breast cancer metastasis through the invasive phenotype by NOV/CCN3 targeting [Yang et al., 2017], and while it should be up-regulated to accomplish its role, it was down-regulated in this study. Antitumor activity is also a feature of miR-99a, which is achieved in human cancer breast cells by targeting the mTOR/p-4E-BP1/p-S6K1 pathway, and in humanurothelial and carcinoma cells found in the urinary bladder by activating the RAD001- triggered apoptotic pathway [45]. These outcomes are connected, according to the findings of this study

Moreover, Gao et al. [46] reached to the indication that "hsamiR206" crush the invasion &proliferation of cells of BCvia Cx43 targeting. This micro-RNA also suppress the metastasis &stamensof BC by MKL1/IL11 targeting pathway [47]. However, Zhou et al. [48] indicated that down-regulated which found in cells of breast cancer can suppress the proliferation of cells through"cyclinD2" up-regulation, and these results are matching with our results.

miRNA profiling studies in transcriptional expression across cancer cell lines and tumor tissues have showed that "miR-29a" down-regulates cancers majority and the opposite thing in the minority.It controls invasion and growth of ER-positive breast cancer cell. [49]. However, different study showed that enforced expression of"miR-29a" control apoptosis by the way of expression of"MCL-1" that inhibiting the ALCL cell lines, at the same time reduction of tumor growth occurs. Subsequently,"miR-29a"synthesis could workas a new diagnosis tool for cancer early diagnosis [51].

. Having the capability to suppress the migration and proliferation of astrocytoma cells, and Furthermore, miR-145 is a dual-stranded tumour suppressor that operates via "MTDH" targeting in lung squamous cell carcinoma and via direct or indirect "TGF-1" regulatory expression to restrict the migration and proliferation of cells in breast cancer[52] kidney cell invasion which is carcinogenic"PAK5- miR-106a-5p" could be used as a suppressor for the potential of . tumor [53]. The function of this is matching with its weak expression and appearance in breast cancer as mentioned in this current study.

Conclusion

About 95 total "miRNAs" were analysed in MCF-7 BC cells in this study. Based on RT-PCR data, approximately 6 of the 95 total "miRNAs" were found to be up-regulated in breast cancer cells, while approximately 26 were found to be down-regulated.

, further investigations need to be done to reach deeply identification the main miRNA role in breast Up-regulated miRNAs such as "hsa -miR-21-5p, hsa -miR-10a-5p, has-miR-23b-3p, hsa -miR-223-3p, unisp -31pc, and unisp-3pc" can be employed as biomarkers for breast cancer early detection based on disease prediction. Finally, we conclude that the significantly up-regulated miRNA"has-miR-23b-3p" could be exploited as a possible diagnostic cancer progression..biomarker in breast cancer

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Conflict of Interest

No cnoflicts of interest the authors have to declare.

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