Section A-Research paper
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Insilco analysis of AGR3 as a predictive biomarker potential in Breast Cancer patients

Priyanka Mishra, Sivakumar Kandula, Satyanarayana Swamy Cheekatla*

Department of Biotechnology, School of Sciences, GITAM(Deemed)University,Visakhapatnam-530045, India
Email: pmishra@gitam.in
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Abstract

The most prevalent ailment in women and the primary reason of mortality globally is breast cancer. Breast cancer membrane protein 11, also known as anterior gradient 3 (AGR3), is excessively expressed in breast cancer and has a crucial function in carcinogenesis. Estrogen, progesterone receptors, and a lower tumor grade are strongly correlated with AGR3 expression in breast cancers. Plasma AGR3 protein concentrations may serve as a diagnostic indicator of early breast cancer. The UALCAN cancer database and Breast Cancer Gene-Expression Miner (bc-GenExMiner) databases were employed to examine the expression of AGR3 in breast cancer and to investigate the relationship between the expression level of AGR3 and clinical markers, including prognostic information in breast cancer. AGR3 expression was elevated in many breast cancer subtypes. According to the KEGG pathway and the Panther pathway, AGR3 is essential for nitrogen metabolism enrichment and glutamine glutamate conversion, respectively. Nitrogen is obtained through nitrogen metabolism, which is used by cancer cells to build nucleotides and proteins. Additionally, also cancer cells rely on the breakdown of glutamine to provide the metabolic intermediates necessary to maintain their bioenergetic and biosynthetic requirements. Next, UALCAN's investigation of the related genes for AGR3 revealed that the genes tetraspanin 13 (TSPAN13) and single-pass membrane protein with coiled-coil domains 4 (SMCO4) have Pearson correlation values of 0.58 and -0.49, respectively. This bioinformatics study suggests that AGR3 may be a biomarker for predicting the outcome of breast cancer. More investigation and clinical trials are necessary to clarify the significance of AGR3 in the treatment of breast cancer.

Introduction

Based on the presence or absence of estrogen and progesterone receptors, as well as human epidermal growth factor 2, breast cancer is categorized into three main subtypes: hormone receptor positive/HER2 negative (70% of patients), HER2 positive (15%–20%), and triple-negative (15%) (Waks and Winer, 2019). Breast cancer progression is a multi-stage process

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involving several types of cells, and prevention is still challenging globally (Sun et al., 2017). Recent advances in liquid biopsy diagnostics and data that clearly demonstrate the potential use of AGR3 as biomarkers for early detection of human breast cancer based on blood tests have rekindled interest in blood or plasma based early breast cancer diagnosis (Garczyk et al., 2015). The AGR3 gene produces a protein that is a member of the endoplasmic reticulum (ER) family of disulfide isomerases (PDI) that catalyzes protein folding and thiol-disulfide interchange events. The encoded protein has a catalytically active thioredoxin domain, an N-terminal ER-signal sequence, and a C-terminal ER-retention sequence. In cases of breast, ovarian, and prostate cancer, this gene is overexpressed. It was discovered that extracellular AGR3 (eAGR3) controls the adherence and migration of tumor cells. But nothing is understood about how AGR3 works. So, the purpose of the current study is to look at how AGR3 affects breast cancer. By thoroughly analyzing the clinical indications in multiple sizable online databases using bioinformatics, we assessed the importance of AGR3 gene expression and its correlated genes TSPAN13 and SMCO4 in breast cancer.

Method

UALCAN analysis

The bioinformatics portal UALCAN (http://ualcan.path.uab.edu) was used to retrieve AGR3 RNA and protein levels in healthy breast tissue and BRCA patients. Data from The Cancer Gene Atlas (TCGA) containing the transcriptome data by RNA sequencing (Wang et al., 2016) and the Clinical Proteomic Tumor Analysis Consortium (CPTAC) Confirmatory/Discovery datasets containing proteomics data by mass spectrometry are used in this expression analysis resource (Whiteaker et al., 2014). We examined AGR3 gene and protein expression, as well as AGR3 promoter methylation levels, in healthy and breast cancer patients. We also looked at AGR3 expression in different types of breast cancer. Using heat maps, we looked for AGR3 genes that were positively and negatively correlated in normal and BRCA tumor cells.

Breast cancer gene-expression miner

The Breast Cancer Gene-Expression Miner (bcGenExMiner v4.3, http://bcgenex.centregauducheau.fr/BC-GEM) was used to analyze the correlation of AGR3 expression with identified co-expressed gene groups that are associated. The correlation module was used to generate the correlation of AGR3 with Tetraspanin 13 (TSPAN13) and Single-Pass Membrane Protein with Coiled-Coil Domains 4 (SMCO4).

UCSC Xena

Xena is a visual exploration tool for all types of multi-omic data and related annotations that is web-based and accessible at http://xena.ucsc.edu. The heat map of AGR3, TSPAN13, and

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SMCO4 was made using data analysis in The Cancer Genome Atlas (TCGA) of Breast Cancer using the UCSC Xena browser.

Gene Expression Profiling Interactive Analysis dataset

Gene Expression Profiling Interactive Analysis (GEPIA) is a newly designed interactive web service that uses a common processing pipeline to examine the RNA sequencing information for 9736 cancer samples and 8587 healthy samples from the TCGA and Genotype-Tissue Expression (GTEx) studies. Customizable GEPIA applications include analyses of tumor or normal differential expression, cancer type or pathological stage profiling, analyses of patient survival, identification of related genes and correlation analysis. The GEPIA database was used to examine the expression of AGR3, TSPAN13, and SMCO4.

LinkedOmics dataset

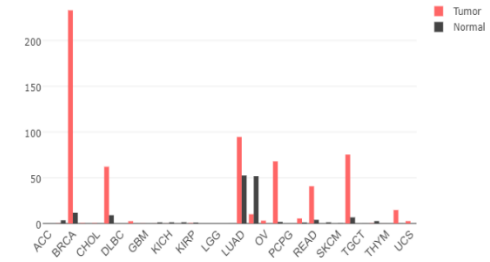
LinkedOmics (http://www.linkedomics.orglogin.php) is a novel software application for sharing data from large-scale cancer omics investigations. It attempts to focus on the identification and study of attribute correlations between patients with various forms of cancer and their risk of acquiring incurable disease. The LinkedOmics Dataset carried out the GSEA analysis of AGR3 gene.

Results

The expression of AGR3 is increased in breast cancer patients

Firstly, Figure 1A displayed how the expression of AGR3 varies between tumour and normal samples. The outcome showed that, the expression level of AGR3 was greater in BRCA tumors than the corresponding normal tissue. The UALCAN cancer database discovered that the expression of AGR3 mRNA and protein levels were larger in cancerous breast tissues than in healthy breast tissues. (Figure 1B-C). The p-value less that 0.01 is considered.

A.



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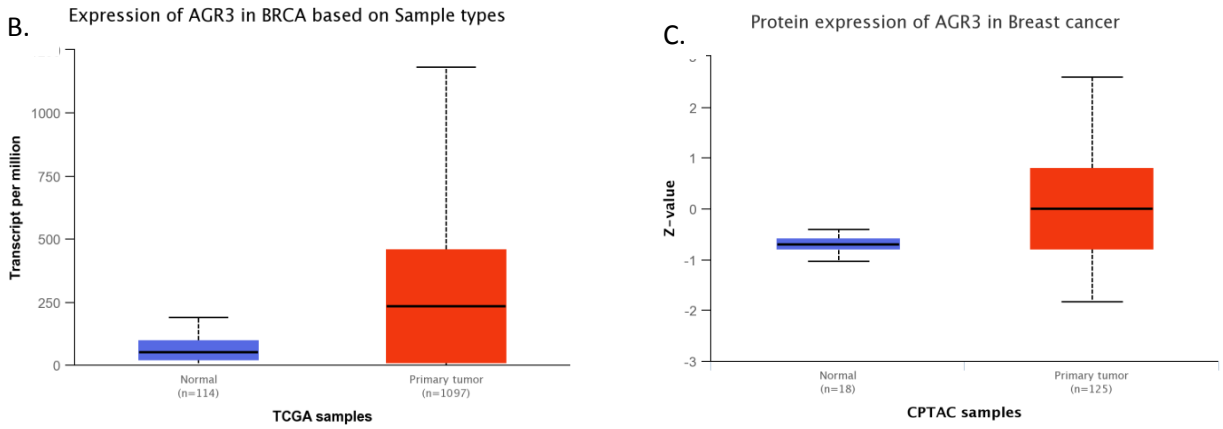

Figure 1: The expression of AGR3 in BRCA by UALCAN. A. AGR3 expression levels in various cancers; **B**. The mRNA expression of AGR3 in primary breast cancer and normal tissues from TCGA samples (p-value = <1E-12), **C.** The protein expression of AGR3 in CPTAC samples of primary breast cancer and healthy tissues (p-value = 4.35812201967263E-07).

The association between AGR3 expression and clinical markers in patients with breast cancer

Next, we analyzed AGR3 expression across patient groups based on several clinical markers using the UALCAN online tool. When compared to the normal group's expression of AGR3, the tumor sample's expression of promoter methylation was noticeably lower (Figure 2A). Additionally, it was discovered that premenopausal and postmenopausal BRCA patients had lower levels of promoter methylation than the normal group had (Figure 2B). It's interesting to note that Luminal BRCA samples have significantly lower promoter methylation than HER2 and TNBC samples. The Scarff-Bloom-Richardson (SBR) is a histological grade that assesses tubule development, nuclear characteristics of pleiomorphism, and mitotic index using the online programme bc-GenExMiner. Patients with breast cancer who had a higher SBR grade tended to exhibit less AGR3 (Figure 2D). Progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor-2 (HER-2) status were all positively linked with AGR3 expression (ER) (Figure 2E-G). Additionally, we discovered that stage 1 and the luminal subtype had much higher levels of AGR3 than other stages and subtypes (Figure 2 I-J). The p value in each of the aforementioned situations is less than 0.01.

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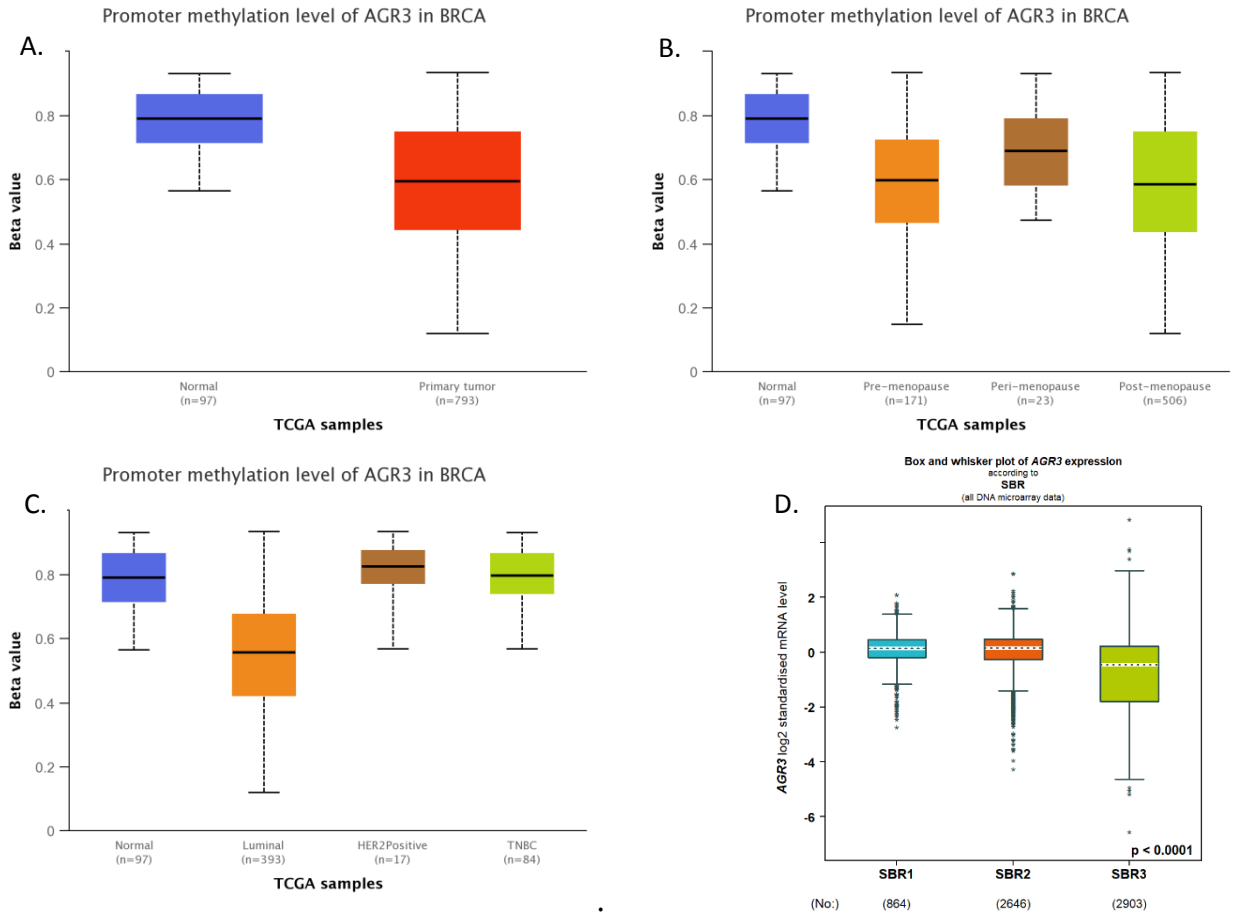

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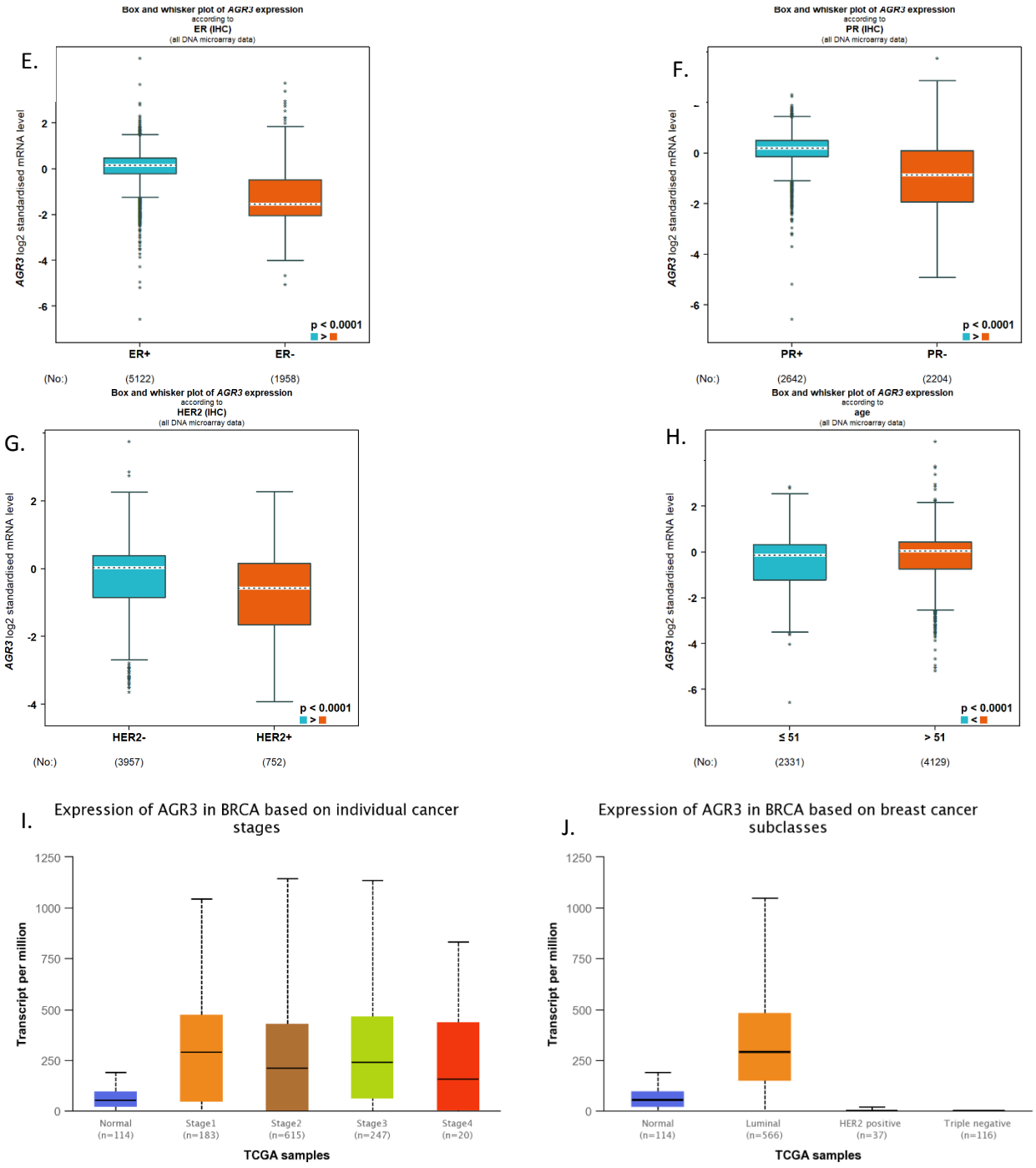

Figure 2: Box plot illustrating how AGR3 expression is related to various clinical indicators. **(A)** promoter methylation level of AGR3 in BRCA (p-value<1E-12), **(B)** promoter methylation level of AGR3 in BRCA based on menopause (p-value of Normal-vs-Pre-menopause<1E-12, p-value of Normal-vs-Peri-menopause is 2.283600E-03, p-value of Normal-vs-Post-menopause is 1.62447832963153E-12) **(C)** promoter methylation level of AGR3 in BRCA based on cancer types (p-value of Normal-vs-Luminal is <1E-12), **(D)** SBR grade of

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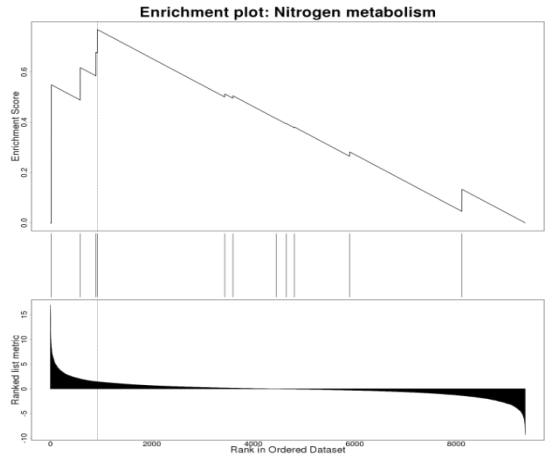
AGR3 in BRCA based on subtypes, **(E)** AGR3 expression according to ER, **(F)** AGR3 expression according to PR, **(G)** AGR3 expression according to PR, **(H)** AGR3 expression according to age, **(I)** expression of AGR3 on individual cancer stages in BRCA (p-value of Normal-vs-Stage1 is 1.62447832963153E-12, Normal-vs-Stage2 is <1E-12, Normal-vs-Stage3 is <1E-12, Normal-vs-Stage4 is 7.142500E-03), **(J)** expression of AGR3 on cancer subclasses in BRCA(p-value of Normal-vs-Luminal is 1.62436730732907E-12, Normal-vs-HER2+ is 2.06289999971077E-07, Normal-vs-TNBC is 1.56309998278203E-09)**.**

Gene set enrichment analysis for AGR3 expression in BRCA

The pathways enriched were searched using GSEA to determine the probable role of AGR3. The outcomes showed that nitrogen metabolism was enriched with an enrichment score of 0.76885 according to KEGG pathway, and glutamine to glutamate conversion was enriched with an enrichment score of 0.89461 according to Panther pathway (Figure 3A-B). TSPAN13 underwent GSEA as well, and the panther pathway demonstrated that it plays a substantial part in the ionotropic glutamate receptor route with an enrichment score of 0.67852.

A.



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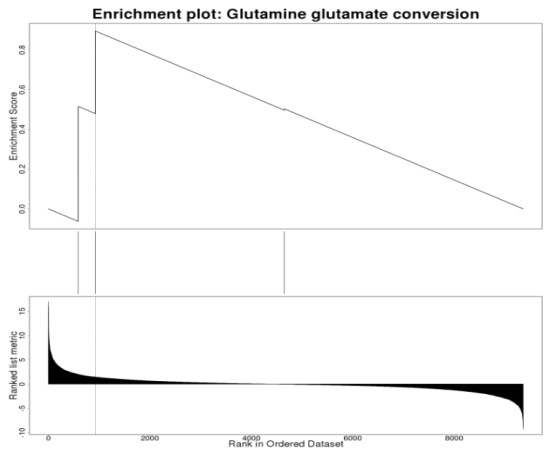

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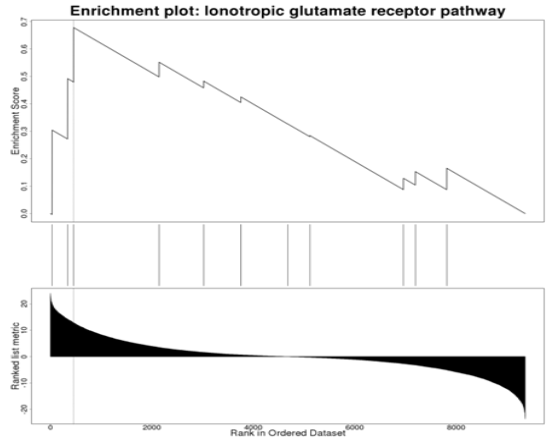

Figure 3: GSEA analysis. The GSEA results showing enrichment plot of AGR3 related gene sets in A. KEGG pathway, B. PANTHER pathway and C. enrichment plot of TSPAN13 related gene sets in PANTHER pathway.

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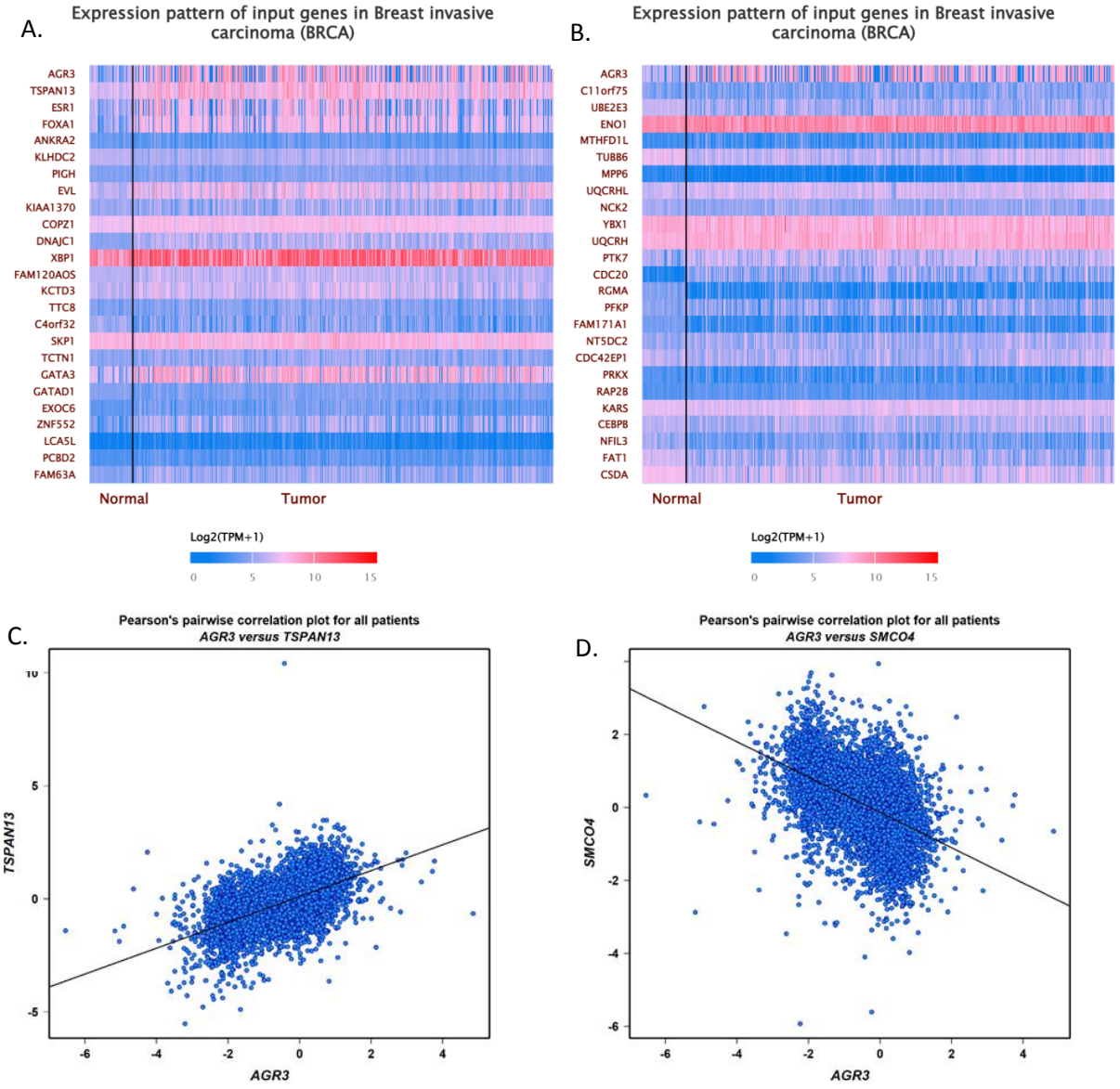
Correlation of AGR3 with TSPAN13 and SMCO4

We created a dynamic heat map of the genes that are differently expressed in normal tissue and BRCAs using UALCAN and included AGR3 as a search gene. The heat-map revealed differences in the expression of several genes, including AGR3, in normal and BRCA tissues (Fig. 4A -B). Further investigation using the bc-GenExMiner database revealed the co-expression profile of AGR3, with TSPAN13 showing a positive correlation (R=0.58, p 0.0001) and SMCO4 a negative correlation (R -0.49, p 0.0001) (Figure 4C-E). According to results from a 50-gene qPCR experiment (PAM50) used to identify breast cancer subtypes in the TCGA database, the expression of AGR3 was shown to be positively connected with TSPAN13 transcript level and negatively correlated with SMCO4 transcript level using UCSC XENA browser (Figure 4F).



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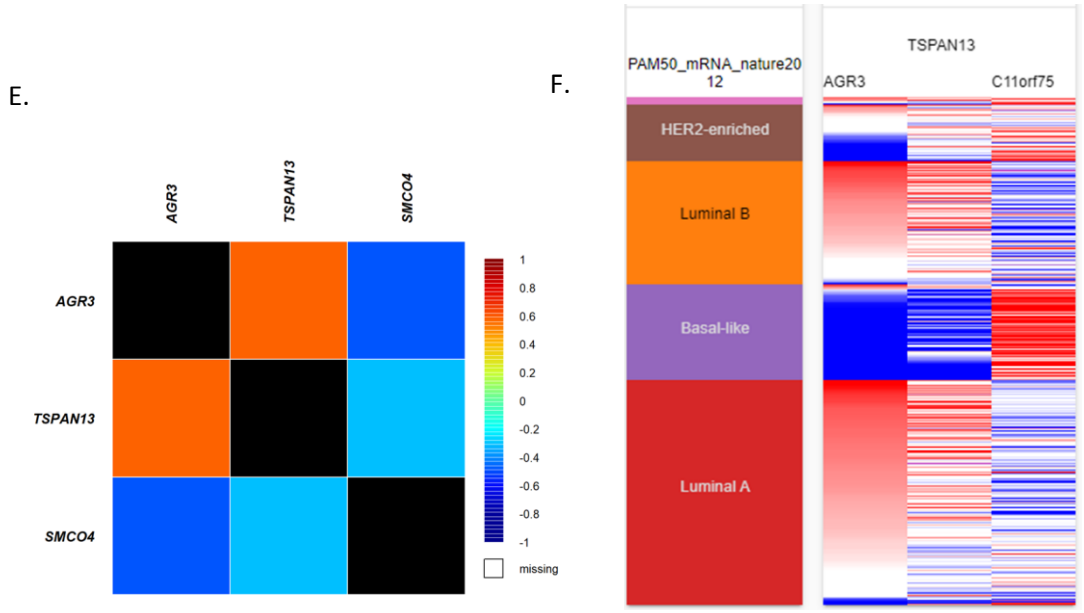

Figure 4: Differentially expressed genes of AGR3 and co-expression analysis of TSPAN13 and SMCO4. (A.) Using data from the online portal UALCAN, a heat-map depiction of the 25 genes of AGR3 that are positively expressed in BRCAs and normal breast tissue was created. **(B.)** Heat-map representation of 25 AGR3 genes that are adversely expressed in BRCAs and healthy breast tissue. **(C, D, E)** Showed the correlation plot of AGR3 with TSPAN13 and SMCO4 in breast cancer by the bc-GenExMiner software. **(F.)** The UCSC Xena web-based tool was used to generate a heat map of AGR3 expression together with TSPAN13 and SMCO4 expression across PAM50 breast cancer subtypes in the TCGA database.

The validation of TSPAN13 and SMCO4 in breast cancer

TSPAN13 expression was validated in the GEPIA database. In contrast to normal breast cells, luminal breast cancer tissues were shown to have much greater levels of TSPAN13, with a significant p value < 0.05. (Figure 5A). In case of SMCO4, it was discovered that the SMCO4 gene was down-regulated in luminal breast cancer cells, although the variation was not statistically significant.

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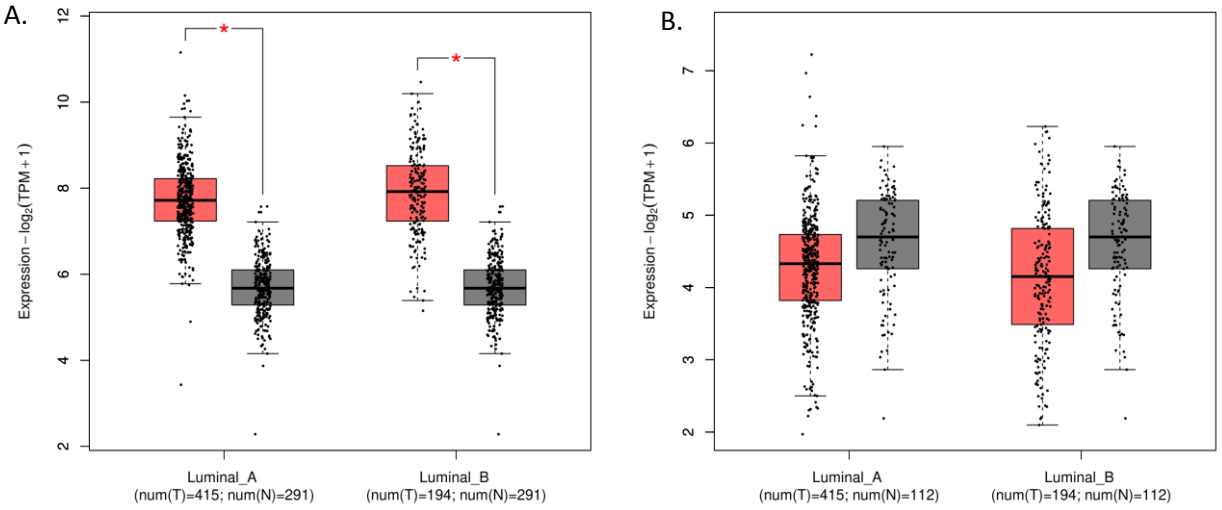

Figure 5: The expression data indicating the potential function of (A) TSPAN13 and (B) SMCO4 in breast cancer by GEPIA database.

Discussion

Carcinogenesis is a multi-step procedure involving changes to the genome that disrupt essential cellular processes of growth and development (Osborne et al., 2004). Multiple genetic events that can activate prevalent oncogenes and impair the activity of particular tumor suppressor are involved in the progression of breast cancer (Lee and Muller, 2010). Many of the molecular pathways underlying the growth of breast cancer are still poorly understood, and existing histological prognostic markers have limited usefulness in predicting the course of the illness. This shortcoming has sparked intense interest in the search for new breast cancer prognostic indicators (Heneghan et al., 2009).

It is possible that AGR proteins play a role in intracellular and extracellular compartments because the human anterior gradient protein AGR3 is overexpressed in a number of adenocarcinomas and is frequently released in cancer patient specimens. The level of differentiation, slowly growing tumors, and a better prognosis for breast cancer patients are all related to AGR3 (Obacz et al., 2015). AGR3 was up-regulated in the luminal subtype of IDC patients with histological grades I–II and was linked with increased chances of distant metastasis and recurrence. AGR3 might encourage breast cancer cells' ability to proliferate and invade (Xu et al., 2019). AGR3 is linked to benign tumors and may serve as a marker for breast cancers that are less aggressive (Prihantono et al., 2021). Uncertainty exists about the significance of AGR3 expression in breast cancer prognosis. This is the first research to identify the AGR3 and its correlated genes TSPAN13 and SMCO4 as possible biomarkers for breast cancer prognosis.

In our investigation, we used the UALCAN database to evaluate the expression profile of AGR3. Compared to normal tissues, breast cancer has higher levels of AGR3 expression. Additionally,

we used the UALCAN database tool to examine the promoter DNA methylation state and found that the promoter methylation of AGR3 was reduced in breast tumors in various breast cancer subtypes when compared to normal tissues. We discovered a correlation between decreased AGR3 promoter methylation and luminal breast cancer, which supports the idea that increased AGR3 gene expression may, at least in part, contribute to the development of luminal cancer. ER, PR, HER-2, and age status were strongly linked with AGR3 expression, according to the online programme bc-GenExMiner. In contrast to normal tissues, SBR status is inversely correlated with AGR3 level in breast cancer samples. The Scarff-Bloom-Richardson (SBR) grade, a significant prognostic factor in breast cancer, was linked to cell proliferation, a reliable sign of metastasis. Additionally, stage I breast cancer had higher levels of AGR3 expression than stage IV. Also, when compared to triple negative and Her2 breast cancer, luminal breast cancer displayed higher levels of AGR3 expression. These findings suggested that AGR3 expression may predict the prognosis of early luminal A and luminal B breast tumors.

The role of AGR3, which is enhanced in nitrogen metabolism and the glutamine-glutamine pathway, was identified by GSEA analysis in breast cancer. In the event of progressive tumor growth, the neoplastic tissue would extract amino acids from the bloodstream more quickly than normal cells would, creating the equivalent of a nitrogen trap (Fenninger and Mider, 1954). Many malignancies rely on glutamine catabolism for metabolic intermediates that sustain bioenergetic and biosynthetic needs. (Cheng et al., 2011). Glutaminase (GLS), a mitochondrial enzyme, initiates this process by converting glutamine to glutamate as part of the glutaminolysis pathway, which is then used in a variety of reactions that support tumor cell growth and survival ("Glutaminase - an overview | ScienceDirect Topics," n.d.). It also includes energy production (TCA cycle), amino acid synthesis, and glutathione production (Kodama et al., 2020). Our findings are the first to suggest a link between AGR3 and nitrogen metabolism and glutamine glutamate conversion signaling pathways in breast cancer. Glutamine is the most common amino acid that our bodies produce, use, and rely on to stay healthy. It can also be found in both animal and plant protein. Glutamate, like glutamine, is a non-essential amino acid that is produced by glutaminase enzymes. Glutamate receptors are clearly found on cancer cells, according to evidence. When a cancer cell is unable to be fueled by glucose, it switches to glutamate. Breast cancer cells produce a lot of glutamate. Glutaminase inhibitors prevent glutamine from being converted to the cancer fuel glutamate by the enzyme glutaminase. Cancer cells stop growing and spreading when glucose uptake and glutamate production are both inhibited.

The co-expression of AGR3 was investigated using the web-based tools bc-GenExMiner and UCSC Xena. AGR3 and TSPAN13 expression exhibited a positive correlation, but SMCO4 and AGR3 exhibited a negative correlation. According to the data presented above, A key player in breast cancer is the molecule TSPAN13. TSPAN13 participates in cell survival through apoptosis and cell-cycle arrest. By altering intracellular signaling pathways like mTOR, Akt, ERK, Bcl-2, and Caspase 3, TSPAN13 stimulates the development of breast cancer (Zhou et al., n.d.). Previous research discovered that tetraspanin NET-6, and CD151 expression was higher in

tumours than in normal epithelial cells. HER2, ER, and PR status, tumour grade, Ki-67 scores, invasion, and metastasis were all associated with the cellular expression of both markers (Jiang et al., 2019). TSPAN13 ectopic expression in breast cancer cells has been shown to inhibit anchorage independent growth, increase apoptosis, and decrease invasion (Huang et al., 2007). In Esophageal Squamous Cell Carcinoma, SMCO4 could be proto-oncogenes (Jumai et al., 2022). It was also discovered that SMCO4 is more highly expressed in ER-negative/HER2-negative breast cancer samples than in ER-positive/HER2-negative breast cancer samples (Shao et al., n.d.). Although there hasn't been much research on SMCO4, our work indicates that it plays an important role in the emergence of cancer. With co-expressed TSPAN13 and SMCO4, AGR3 might be regarded as a prognostic biomarker for breast cancer prognosis. More research and clinical trials are needed to determine the efficacy.

Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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