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Gene Expression Profiling of FOXC1 and MMP-7 in Breast Cancer and Fibroadenoma in Basrah – South Iraq: A Comparative Study

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Abstract

Introduction. Globally, Breast cancer (BC) continues to be a predominant factor in cancer-related fatalities worldwide, and metastases drastically lower patient survival rates. Both matrix metalloproteinase-7 (MMP-7) and forkhead box C1 (FOXC1) are recognized as critical modulators of tumor invasion and dissemination.
Purpose. This research aimed to evaluate and compare the transcriptional activity of MMP-7 and FOXC1 across different breast lesion types in the tissue of patients with fibroadenoma and BC in Basrah, South Iraq.
Materials and methods. Between January 2024 and January 2025, 23 fibroadenoma samples and 37 BC tissue biopsies were gathered for a comparative analysis. Using β-actin as an internal control, FOXC1 and MMP-7. The level of gene transcription was evaluated employing quantitative real-time polymerase chain reaction (qPCR) methodology. To ascertain the significance of expression differences across groups, statistical analysis was conducted.
Results. In this study the Patients with fibroadenoma had an average age of 35.3 years, but those with BC had an average age of 45. Compared to fibroadenoma, BC tissues exhibited considerably higher levels of FOXC1 expression (2.6-fold increase, $p<0.05$). Additionally, samples of BC had significantly higher MMP-7 expression, which was 4.4 times higher than that of fibroadenoma ($p<0.05$). Because of the small sample size, there was no discernible correlation between MMP-7 expression and tumor grade.
Conclusions. When compared to benign fibroadenoma, both FOXC1 and MMP-7 are markedly elevated in BC, demonstrating their significance as molecular indicators and potential intervention points in oncology. These results emphasize the significance of FOXC1 and MMP-7 in tumor growth and aid in the molecular characterization of BC in the Basrah community. It is advised that these biomarkers be validated and their clinical value investigated in larger cohort studies.
Keywords: FOXC1, BC, fibroadenoma, MMP-7, qPCR

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Профилирование экспрессии генов FOXC1 и MMP-7 при раке молочной железы и фиброаденоме в Басре, Южный Ирак: сравнительное исследование

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Резюме

Введение. Во всем мире рак молочной железы (РМЖ) занимает 1-е место среди онкологической смертности, а метастазы значительно снижают показатели выживаемости пациентов. Матриксная металлопротеиназа-7 (ММП-7) и фактор транскрипции FOXC1 (FOXC1) признаны критически важными модуляторами инвазии и распространения опухоли.
Цель. Данное исследование направлено на оценку и сравнение транскрипционной активности ММП-7 и FOXC1 в тканях при различных типах поражений молочной железы у пациентов с фиброаденомой и РМЖ в Басре, Южный Ирак.
Материалы и методы. В период с января 2024 г. по январь 2025 г. для сравнительного анализа были собраны 23 образца фиброаденом и 37 биопсий тканей при РМЖ. В качестве внутреннего контроля использовался β-актин, а уровень транскрипции генов FOXC1 и ММП-7 оценивался с помощью количественной ПЦР в реальном времени (qPCR). Для определения значимости различий в экспрессии между группами был проведен статистический анализ.
Результаты. В данном исследовании средний возраст пациентов с фиброаденомой составил 35,3 года, а пациентов с раком молочной железы – 45 лет. По сравнению с фиброаденомой, ткани РМЖ демонстрировали значительно более высокий уровень экспрессии FOXC1 (увеличение в 2,6 раза, $p<0,05$). Кроме того, образцы РМЖ имели значительно более высокую экспрессию ММП-7, которая была в 4,4 раза выше, чем при фиброаденоме ($p<0,05$). Из-за небольшого размера выборки не было выявлено заметной корреляции между экспрессией ММП-7 и степенью злокачественности опухоли.
Выводы. По сравнению с доброкачественной фиброаденомой, уровни FOXC1 и ММП-7 значительно повышены при РМЖ, что демонстрирует их значимость в качестве молекулярных индикаторов и потенциальных точек воздействия в онкологии.

Эти результаты подчеркивают значимость FOXC1 и ММП-7 при росте опухоли и помогают в молекулярной характеристике РМЖ в сообществе Басры. Рекомендуется провести валидацию этих биомаркеров и исследовать их клиническую ценность в более крупных когортных исследованиях.
Ключевые слова: FOXC1, рак молочной железы, фиброаденома, ММП-7, qPCR

■ INTRODUCTION

Globally, BC remains a predominant contributor to cancer-associated deaths, with metastasis being the primary driver of poor clinical outcomes [1, 2]. Distant metastases drastically lower five-year survival rates to about 27%, despite early-stage BC having very favorable survival rates. In order to improve patient outcomes by early detection, risk stratification, and focused treatment approaches, it is imperative to comprehend the molecular pathways behind metastatic development [3].

Tumor cell invasion, intravasation into circulation, survival in the bloodstream, extravasation at distant sites, and development of new tumors are all steps in the intricate, multi-step metastatic cascade. Complex molecular networks that include inflammatory mediators, proteolytic enzymes, and transcription factors coordinate this process [4, 5].

Forkhead box C1 (FOXC1) has been recognized as a pivotal molecular factor implicated in the metastatic behavior of breast carcinoma. It actively promotes the epithelial-to-mesenchymal transition (EMT), a fundamental biological process that enhances the invasive and migratory properties of malignant cells [6]. Mechanistically, FOXC1 suppresses epithelial markers while activating transcriptional programs that improve cell motility, invasion, and resistance to apoptosis [7, 8]. According to clinical research, individuals with BC who have higher levels of FOXC1 expression had worse prognoses, a higher risk of metastases, and a shorter disease-free life. Moreover, basal-like breast tumors, which tend to be more aggressive and have fewer treatment choices, are linked to FOXC1 expression [6, 9, 10]. Matrix metalloproteinase-7 (MMP-7) is essential for the development of BC because it breaks down extracellular matrix elements and promotes tumor cell invasion. In contrast to other MMPs, MMP-7 cleaves a variety of matrix proteins, such as collagen IV, laminin, and fibronectin, demonstrating a rather broad substrate specificity [11, 12]. In addition to degrading the matrix, MMP-7 processes growth factors and cell surface proteins to activate pro-metastatic signaling pathways. In BC, enhanced expression of MMP-7 has been associated with poor clinical outcomes, lymph node metastases, and enhanced invasiveness [13]. The enzyme is a desirable biomarker for determining metastatic risk because of its simultaneous involvement in both distant metastasis and local invasion [14].

Accordingly, this study seeks to investigate the relationship between MMP-7 and FOXC1 gene expression across different stages of BC and to compare these patterns with those observed in fibroadenoma cases.

■ MATERIALS AND METHODS

Study design

A total of 37 breast tissue biopsies were collected from patients diagnosed with BC prior to receiving any treatment, during the period from January 2024 to January 2025.

For comparison, 23 breast tissue biopsies were also obtained from patients diagnosed with fibroadenoma within the same timeframe.

Inclusion criteria

1. Patients with newly diagnosed primary BC (Not receiving any treatment yet).
2. Patients with Fibroadenoma.

Exclusion criteria

1. Recurrent or metastasis BC.
2. Other malignancy.
3. Autoimmune disease.

Data Collection

After crossing data from the center with the hospital laboratory data the researcher followed the confirmed cases by obtaining information from their related files. Data is transported from each patient file into a prepared paper form (questionnaire) that was prepared by the researcher and included the following:

1. Patients demographic data of Age, Parity and body mass index.
2. Past medical history: history of associated comorbidities including: hypertension, diabetes, ischemic heart disease, thyroid disease, and others.

All samples were handled under standardized conditions as in Tuama et al. [15] and applied immediately in a tube contain RNA later solution to ensure tissue integrity for subsequent analyses. Utilizing the Vivantis Technologies Sdn Bhd kit (Malysia). Total ribonucleic acid was purified from fresh biological tissue samples and FFPE followed the instructions manuals by the manufacturer. Using the 5x RT Master Mix supplied by Tinzyme Co., Limited (China), the synthesis of cDNA was performed on the isolated RNA samples in the manner described by the manufactures. To determine the expression levels of the FOXC1 and MMP7 genes, Quantitative real-time PCR utilizing SYBR Green dye was employed to amplify the synthesized cDNA. using forward and reverse primers specific to a gene (for both target genes) as Kong, et al. [16] β-actin, a housekeeping gene, served as an internal regulator for normalization. All reagents were supplied by Macrogen Company. The program for the amplification of the genes of interest included in the current study as follow: Denaturation at 95 °C, Annealing 60 °C for sixty second, then extension at 72 60 °C for sixty second with 40 rounds. The Ct evaluations for each target gene (FOXC1 and MMP7) as well as for the housekeeping gene (β-actin), were performed.

■ RESULTS

The observations reported in this study regarding the age of the participants displayed that the mean age of BC group (BC is 45 (27–76) year and the mean age of patients with fibroadenoma (FA) is 35.3 (16–51) years. Regarding the BC group 20 patients within grade II (54.1%) while the remaining 17 diagnosed with grade III 45.9%.

Demonstrated that FOXC1 expression levels were significantly higher in BC samples when compared with FA specimens ($P<0.05$) as in figure 1A. The FOXC1 gene expression in BC is 2.6 times higher than in group of FA, indicating a significant upregulation in BC patients ($P<0.05$), (Figure 1B). SYBR green and MMP-7-specific primers were utilized to comparatively evaluate the gene expression of MMP-7, which is implicated in numerous

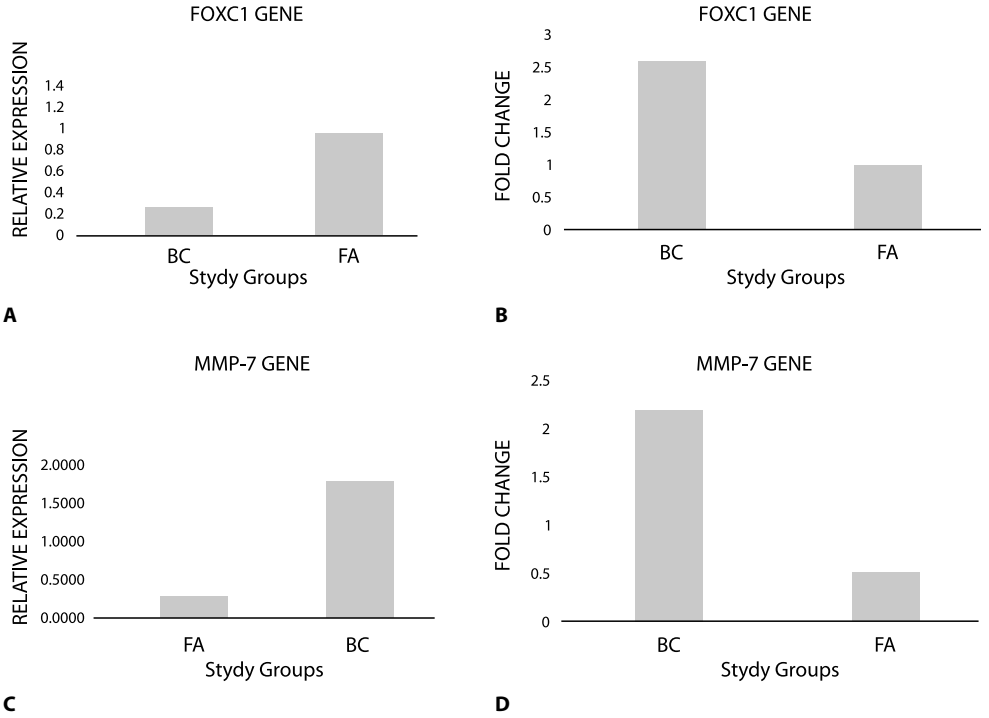

Fig. 1. A – The expression level of FOXC1 in both BC and FA samples; B – Fold change analysis of FOXC1; C – The expression level of MMP-7 in both BC and FA samples; D – Fold change analysis of MMP-7

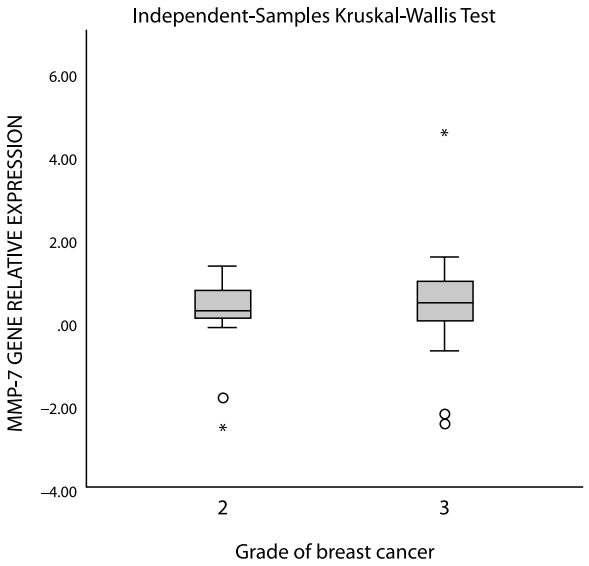

Fig. 2. The association of MMP-7 gene expression with the grade of BC

diseases. The findings demonstrated that MMP-7 expression was markedly elevated in BC cases compared to fibroadenoma samples. after deducting the housekeeping gene signal as in Figure 1C. Significant elevation of the MMP-7 gene in malignant breast tissue is indicated by the about 4.4-fold increase in MMP-7 gene expression in BC as opposed to fibroadenoma (FA) (Figure 1D).

MMP-7 overexpression is demonstrates a close association with the aggressiveness and development of tumors (Figure 2).

■ DISCUSSION

BC is regarded as a common malignancy among all other cancer kinds worldwide [17]. The current study reported that females with BC had marked upregulation in the expression of FOXC1 gene than those had fibroadenoma, this in agreement with Elian et al. [18] and Wang et al. [19]. According to Elian et al. [18], members of the FOX family are strongly associated with carcinogenesis, and some FOXC protein members have a significant influence on the development and therapeutic resistance of malignancies.

The initial evidence highlighting the functional role and prognostic significance of FOXC1 in malignancy was first introduced in BC research in 2010 [6]. Subsequent findings have established that elevated FOXC1 expression, whether at the transcript or protein level, serves as a statistically independent indicator of reduced survival rates and increased risk of metastasis. Multiple studies have since substantiated the prognostic utility of FOXC1 as a reliable marker for predicting adverse clinical outcomes [20].

According to earlier research's patients with subtype that associated with the poorest prognosis in breast malignancies, basal-like BC (BLBC), could be reliably identified by their expression of FOXC1. Research has demonstrated that BLBC is a "hidden" diagnosis that is not limited to triple negative breast tumors (TNBCs) and can occur regardless of receptor profile status [6, 21].

Aggressive metastatic cancer characteristics are significantly influenced by FOXC1. FOXC1 has surfaced as a potential master regulator and marker for BC [21]. Patients with bigger tumors and FOXC1 expression were more likely to experience distant metastases or local recurrence, according to [22].

Among patients without lymph node involvement, elevated FOXC1 expression correlated with an increased occurrence of pulmonary and cerebral metastases, as well as a reduction in metastasis-free survival [9].

Matrix metalloproteinases (MMPs) comprise a group of zinc-dependent proteolytic enzymes that facilitate the degradation of the extracellular matrix (ECM) and basal membrane constituents. Normal processes like tissue remodeling throughout development depend on MMPs, but they can promote pathologic states like tumor invasion and metastasis [23].

Fibroadenomas, on the other hand, are benign fibroepithelial tumors that typically exhibit low proliferative activity and lack the aggressive behavior linked to FOXC1 overexpression in malignancies [24–26].

Studies of the gene expression of fibroepithelial tumors, such as fibroadenomas, show that their molecular profiles are very different from those of malignant tumors, and that indicators such as FOXC1 have not been linked to the prognosis or progression of these tumors. Furthermore, FOXC1's function as a predictive biomarker in this benign setting is unknown, and fibroadenomas often do not significantly raise the risk of BC, with the exception of extremely uncommon complex instances [9, 24].

MMP expression is typically relatively low under normal circumstances, Elevated levels of matrix metalloproteinases (MMPs) have been observed across multiple cancer types and are linked to enhanced tumor growth and cellular proliferation [25, 26].

This research investigated the expression levels of the MMP-7 gene in individuals diagnosed with BC. was significantly higher as compare with fibroadenoma $p<0.05$, but no significant association with the grade of tumor due to small sample size.

Many investigations have consistently found that BC cells and tissues have elevated MMP-7 expression. The aggressive form of the illness is closely associated with this overexpression [27].

In almost all solid cancers, Elevated matrix metalloproteinase expression has been associated with reduced overall survival. Research has also demonstrated a strong correlation between increased MMP expression and tumor aggressiveness. For instance, elevated levels of several MMPs, including MMP 7, have been linked to distant metastases from BC [28].

Research has demonstrated that the proliferation and spread of tumor cells may be effectively suppressed through downregulating MMP-7. Additionally, it has been demonstrated that lowering MMP-7 elevated level of apoptosis, which restores a vital process for eradicating malignant cells, and decreases drug resistance, which makes cancer cells more vulnerable to traditional chemotherapies [29, 30].

Future treatment plans are more likely to include combination techniques due to the complexity of BC and its propensity to become resistant to single treatments. By enabling lower doses of individual drugs, integrating MMP-7 inhibitors with currently available targeted treatments, chemotherapy, or immunotherapy may provide synergistic benefits, improving therapeutic efficacy, and reducing resistance mechanisms [13].

Cancer research has looked into MMP inhibition in great detail. Natural proteins called tissue inhibitors of metalloproteinases (TIMPs) selectively block MMPs [12]. Regarding Fibroadenoma which is a benign disorder, and there is no indication that overexpression of MMP-7 affects its prognosis or course.

Although earlier research has demonstrated that FOXC1 promotes cancer cell invasion and metastasis, its exact mode of action is unknown. The induction of EMT by FOXC1 expression may be the cause of the higher invasive capacity that FOXC1 imparted in earlier investigations Nonetheless, the research presented here shows that, even in the absence of EMT, FOXC1 May increase the invasiveness of breast epithelial cell lines [31].

The potential of FOXC1 overexpression to cause invasion and the strong association between MMP7 and FOXC1 expression in in both BC cellular models and tumor tissues indicated that FOXC1 controls MMP7 expression had been provide by Steven et al. [32] and they confirmed that FOXC1 overexpression significantly increased the amount of MMP7.

Han et al. [33] reported that FOXC1 increased matrix metalloproteinase-7 (MMP7) and WNT5A in TNBC cells. The overexpression of MMP7 by FOXC1 is mediated by WNT5A, and the FOXC1-induced invasive behavior of TNBC cells under in vitro conditions depends on the WNT5A-MMP7 axis. NF-κB and MMP7 are key components of the FOXC1-associated triggering of alternative WNT5A pathway, which is crucial for TNBC cell invasiveness and has implications for creating a successful treatment for the disease. Furthermore, Han et al. demonstrated that high levels of FOXC1 serve as a prognostic indicator of unfavorable clinical outcomes across various cancer types [33]. However, different authors from Iraq

didn't such modalities in breast cancers [34–38], gastric cancer [39], CNS tumors [40], anal tumors [41], colorectal cancers [42–44], head and neck carcinoma [45–48], endometrium cancer [49], and ovarian tumor [50].

■ CONCLUSIONS

According to this study, patients in Basrah, South Iraq, had considerably higher levels of the FOXC1 and MMP-7 genes in their BC tissues when compared to samples of benign fibroadenoma. The small sample size in this cohort is probably the reason why there isn't a significant correlation between MMP-7 expression and tumor grade. However, the significant overexpression of both genes in cancerous tissues highlights their potential use in risk assessment and molecular characterization of patients with BC.

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