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RESEARCH ARTICLE

Knockdown of Tyrosine Kinase Receptor FGFR1 via AZD4547 Suppresses Breast Cancer Proliferation, Migration, and Invasion in BRCA1 Mutant Adipose-Derived Stem Cells (ASCs) via IL-6 and TNF-α Modulation

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ABSTRACT

Breast cancer is a complex heterogeneous disease that poses significant challenges in identifying novel therapeutic strategies and new therapeutic targets. Recent research has identified adipose-derived stem cells (ASCs) role in the progression of small tumors. Mutations in Breast Cancer gene 1 (BRCA1) are known to play a crucial role in DNA repair and cell cycle regulation. BRCA1 mutations have been associated with increased risks of breast and ovarian cancer. Moreover, studies have shown that Fibroblast Growth Factor Receptor 1 (FGFR1) is involved in initiation of many cancers, including breast cancer. In the present study, we aim to investigate the role of FGFR1 in BRCA1-negative ASCs and its therapeutic potential in breast cancer. Using AZD4547 to knockdown FGFR1 expression in BRCA1 mutant ASCs in vitro and in vivo. Our results showed that FGFR1 knockdown significantly inhibited the release of pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) from BRCA1 mutant ASCs. Furthermore, FGFR1 knockdown has significantly decreased proliferation, migration, and invasion of breast cancer cells co-cultured with BRCA1 mutant ASCs. Xenograft studies have confirmed reduced tumor growth and metastasis via Vascular Endothelial Growth Factor A (VEGFA) expression inhibition and Nuclear factor kappa-B cells (NF-κB) pathway downregulation. Collectively, our results emphasize the critical role of FGFR1 in BRCA1 mutant ASCs in the progression of breast cancer through inflammatory cytokines regulation. Moreover, our results suggest that targeting FGFR1 in tumor microenvironment, specifically in BRCA1 mutant ASCs, may be a promising therapeutic approach in breast cancer treatment. However, further clinical studies are needed.

Keywords: Adipose-derived stem cells (ASCs), BRCA1 mutations, Fibroblast growth factor receptor 1 (FGFR1), Interleukin-6 (IL-6), Pro-inflammatory cytokines, Tumor necrosis factor-alpha (TNF-α)

Introduction

Breast cancer (BC) is a complicated, heterogeneous disease with a growing burden on women's health worldwide,[1] with nearly 300,000 new instances and 43,000 deaths predicted in 2023.[2] Despite the scientific advancement in early diagnosis, identification, and therapeutic approaches, metastatic breast cancer still poses significant challenges, emphasizing the requirements for alternative therapies. Adipose-derived stem cells (ASCs) are multipotent stem cells that reside in adipose tissue and participate in pathophysiological mechanisms, including cancer progression.[3] These cells secrete numerous growth factors, cytokines, and different signaling molecules that can significantly influence the behavior of neighboring cells, including cancer cells,[4,5] in the latter

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case these cells will promote invasion and metastasis, and contribute to the creation of a supportive tumorigenic microenvironment.[6] Recent review research has highlighted the key role of ASCs in these complicated methods of cancer development and metastasis.[7] Breast Cancer gene 1 (BRCA1) is critical to DNA repair and cell cycle regulation.[8] Individuals with BRCA1 mutations have a higher risk of developing ovarian and breast cancers, and their tumors are frequently highly aggressive and resist treatment.[9] Zhao et al., reported that BRCA1 mutations can affect the function and behavior of ASCs, enhancing the complexity of the tumor microenvironment.[10] Fibroblast growth factor receptor 1 (FGFR1) is a tyrosine kinase receptor that plays an essential role in many cellular mechanisms such as migration, proliferation, and differentiation.[11] Abnormal FGFR1 signaling is found in the growth and progression of many cancer types, including breast cancer.[12,13] However, the precise contribution of FGFR1 in ASCs, particularly in the context of BRCA1 mutations, remains in large part unknown.[13] Inflammation has long been recognized as a hallmark of cancer, and inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) plays an important role in tumor growth, angiogenesis, and metastasis, among others.[14] ASCs are known to release a wide range of inflammatory cytokines, which can affect the behavior of cancer cells and the surrounding microenvironments.[15] Hence, our objective was to examine the function of FGFR1 in ASCs with BRCA1 mutations and its possible use as an effective therapeutic target for breast cancer management. We created FGFR1 knockdown models in BRCA1 mutant ASCs using the AZD4547 gene-editing system, and we carefully examined the effects on the release of pro-inflammatory cytokines, the behavior of breast cancer cells, and the progression of tumors both in vitro and in vivo. Knowing that breast cancer is a major health challenge worldwide, and that BRCA1 mutations are known to increase the risk and aggressiveness of the disease, plus the important role of ASCs in tumor microenvironment, the precise contribution of FGFR1 in ASCs remains unclear, especially for BRCA1 mutations.[1,3,13] This study aims to address this gap by examining the role of FGFR1 in BRCA1 mutated ASCs and its potential as a therapeutic target.

Materials and methods

Cell culture

BRCA1 mutant and wild-type ASCs were purchased from commercial sources, National Research Centre (NRC) and cultured in suitable growth media. ASCs growth media (PT-3273 and PT-4503; Lonza) were used to sustain ASCs. As per the published methodology, the cell media was replaced every three days, and the cells were passaged using 0.5% Trypsin every six days.[16] By cultivating 1 $\times$ 105 ASCs in adaptogenic induction media (PT-3004; Lonza) for 14 days, the maintenance of adipogenesis in the stem cells was verified. Paraformaldehyde (4%); oil red O (O0625; Sigma-Aldrich, St. Louis, Mo.) was used to stain the cells. Breast cancer cell lines (MCF-7) were cultured in Phenol red free DMEM medium with 10% FBS, 0.01 mg/ml bovine insulin, according to established protocols published before.[17]

MCF-7 tissue culture

The American Type Culture Collection (ATCC, HTB-22) provided the human MCF-7 cells. When a confluence of 80% to 90% was attained, cells were sub-cultured at a ratio of 1:3 in 25 cm^2 culture flasks (Corning). We followed the company's culture protocols. Both 2D and spheroid cultures of MCF-7 cells were conducted using phenol red-free DMEM media supplemented with 10% FBS, 0.01 mg/ml bovine insulin, 10 nM estradiol, standard penicillin/streptomycin, and glutamine.[17]

FGFR1 knockdown models in BRCA1 mutant ASCs using AZD4547

AZD4547 getting ready

AZD4547 (N- [5- [2- (3,5-dimethoxyphenyl) ethyl]-1H-pyrazol-3-yl]-4- [(3R,5S)-3,5-dimethylpiperazin-1-yl] benzamide) (AbMole Bioscience, Houston, TX, USA) was prepared in a 2.5% (v/v) solution of dimethyl sulfoxide (DMSO) and polyoxyethylenesorbitan monooleate (Tween-80) in Phosphate Buffered Solution (PBS) for use *in vivo* investigations. AZD4547 was produced as a 1-mM stock solution in DMSO for *in vitro* experiments.

In vitro assays

Inflammatory cytokine secretion (IL-6, TNF-α) from ASCs was measured using ELISA technique by using commercial available kits from My BioSource (San Diego, USA) (Cat number MBS590025) for TNF-α, and (Cat number MBS730957) for IL-6. The assay was carried out in accordance with the manufacturer guidelines. Breast cancer cells proliferation was assessed using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays technique. The MTT assay was used to determine the viability of the cells. A microplate reader was used to detect the reduction of MTT to purple formazan after three hours of incubation with the sample. MC-7 samples were plated in 96-well plates at 5,000 cells per well, and they were treated with or without AZD4547 for

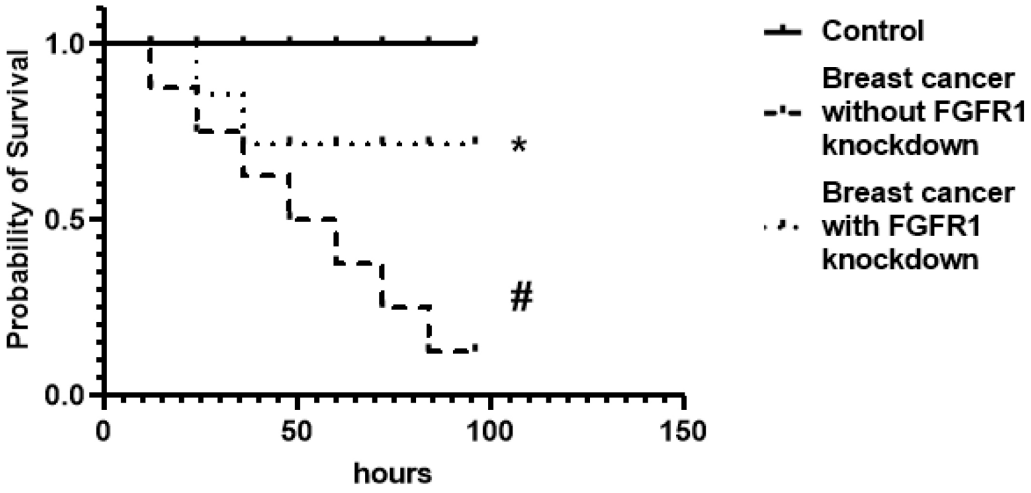

Fig. 1. FGFR1 knockdown increases survival probability in mice with breast cancer.

twenty-four hours. The formula for calculating cell viability was:

Cell viability = A treated / A control × 100%.[18]

In vivo Xenograft studies

Thirty immunocompromised mice (NOD/SCID) were used for xenograft experiments. NOD/SCID immunocompromised mice refers to a SCID mutation that has been transferred onto a diabetes-susceptible Non-Obese Diabetic (NOD) mice models to generate multiple defects in immunity for research purposes. Eight- to ten-week-old male mice (n = 10) were acquired from Shanghai SLAC Laboratory Animal Limited Liability Company (Shanghai, China). A pathogen-free laboratory animal environment with a 12-hour light/dark cycle, an ambient temperature of 23 ± 3 °C, and a relative humidity of 55 ± 10% were used to rear the mice. BRCA1 mutant ASCs (with or without FGFR1 knockdown) were co-injected with breast cancer cells into the mammary fat pads. Tumor growth was monitored over time, and metastatic dissemination was evaluated by evaluation of vascular endothelial growth factor A (VEGF-A) level by ELISA.

Enzyme-linked immunosorbent assay (ELISA)

After twenty-four hours' post-injection, whole blood was drawn without the use of an anticoagulant and allowed to incubate for 30 minutes at room temperature. The serum was obtained by centrifugation at 6000 ×g for 15 minutes, and it was stored at −80°C. The supernatants of RAW264.7 cells were also collected and kept at −80°C until analysis. Using ELISA, the manufacturer's instructions were followed to ascertain the concentrations of cytokines such as IL-6, and TNF-α in the serum and supernatant (Multi Science, China).

Mechanistic studies

Nuclear factor kappa B (NF-κB) signaling pathway activation was analyzed using immunohistochemically assay staining according to the guideline of previous work.[19]

Statistical analysis

All experiments were conducted in triplicate, and data were analyzed utilizing GraphPad Prism 9.0 (GraphPad Software, USA). The means ± standard error of the means (SEM) was used to present all data. One-way analysis of variance (One-way ANOVA) statistical method was used for the statistical analysis of the data followed by Tukey Kramer test. A statistically significant value was defined as $p < 0.05$.

Results and discussion

FGFR1 knockdown improves survival and alleviates systemic inflammation in breast cancer (BC) mice In vivo

A survival analysis was done on BC mice to investigate the impact of FGFR1. In the BC group, the total 96-hour survival rate was 2/10 (20%), but in the BC + FGFR1 knockdown group, it was 8/10 (80%). According to a log-rank analysis, the survival of BC mice that received FGFR1 knockdown prior to treatment was considerably higher than that of the BC group, Fig. 1; $p < 0.01$.

For survival probability testing, three groups of mice were randomly assigned: ten mice each for the untreated control group, ten mice each for the BC group without FGFR1 knockdown, and ten mice each

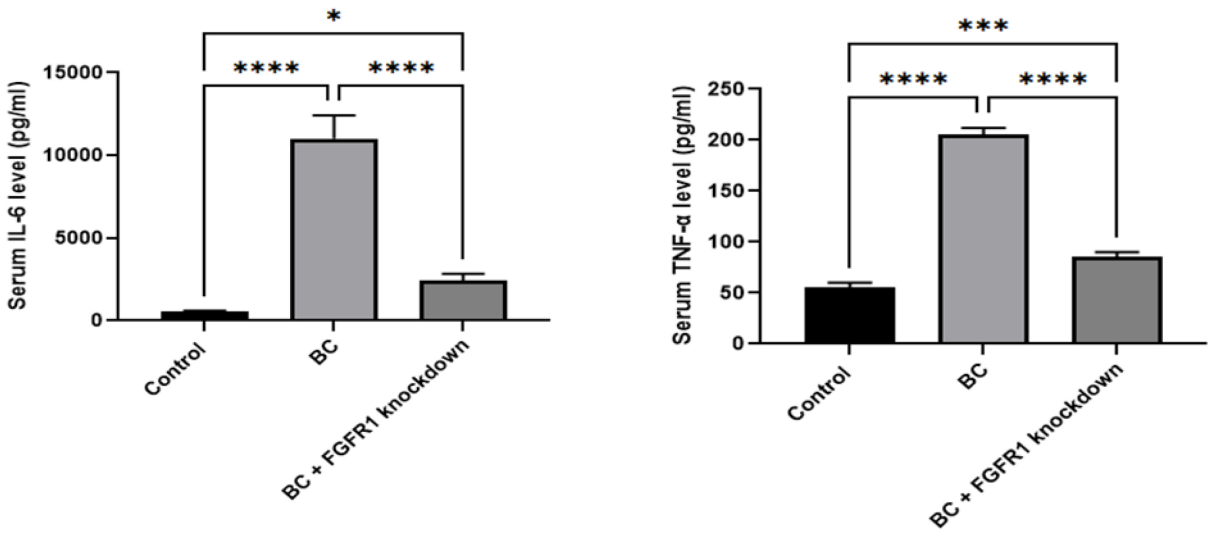

Fig. 2. The level of serum IL-6, and TNF-α in mice with breast cancer w/wo FGFR1 knockdown.

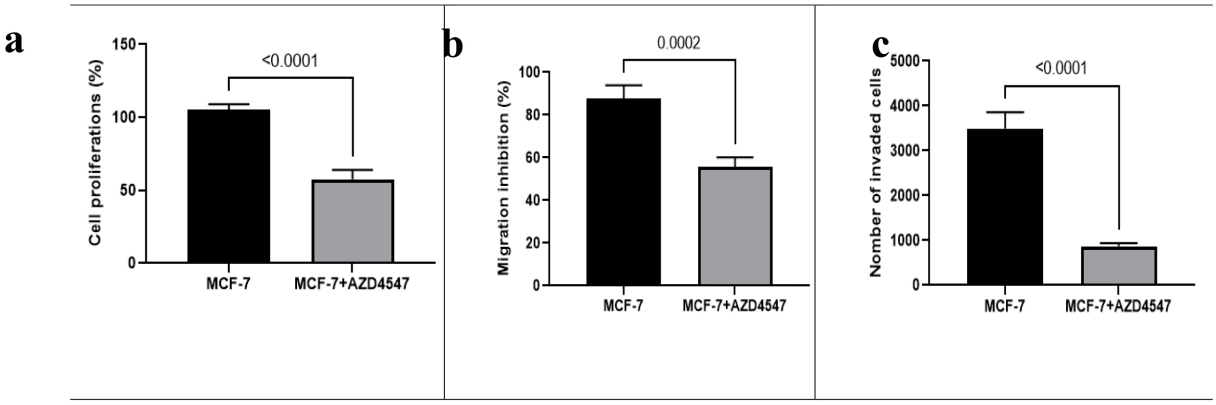

Fig. 3. FGFR1 knockdown suppresses breast cancer cells proliferation, migration, and invasion.

for the BC group with FGFR1 knockdown, and they were processed accordingly. Survival was tracked, and the log-rank (Mantel-cox) test was used to examine variations. The difference between the BC without FGFR1 knockdown group and the untreated control group was marked by a pound sign ($p = 0.064$); the difference between the BC with FGFR1 knockdown group and the BC without FGFR1 knockdown group was denoted by an asterisk ($p = 0.064$) Fig. 1.

The quantities of serum IL-6, and TNF-α were measured by ELISA, Fig. 2. The values were displayed as mean ± standard error (SEM), with *$p = 0.017$ and ***$p < 0.0001$.

One of the primary features of breast cancer is an intense, systemic inflammatory response. ELISA was utilized to measure the levels of serum inflammatory mediators to investigate if FGFR1 knockdown reduced systemic inflammation.

The BC group had significantly increased levels of serum inflammatory-associated cytokines, including TNF-α and IL-6, in comparison to the untreated control group, Fig. 2. As anticipated, the amounts of these inflammatory mediators generated by BC induction were markedly reduced by pretreatment with AZD4547. According to our findings, FGFR1 knockdown shields mice with BC from the systemic inflammatory response brought on by BC.

FGFR1 knockdown suppresses breast cancer cell proliferation, migration, and invasion In vitro

Conditioned media from FGFR1 knockdown BRCA1 mutant ASCs significantly impaired the proliferation, migration, and invasion of breast cancer cells (MCF-7) compared to control ASC-conditioned media. Direct co-culture of breast cancer cells with FGFR1 knockdown BRCA1 mutant ASCs also resulted in reduced cancer cell proliferation, migration, and invasion, Fig. 3.

As seen in Fig. 3a, MCF-7 breast cancer cells proliferation was assessed using a fluorescence cell proliferation test based on resazurin 24 hours following

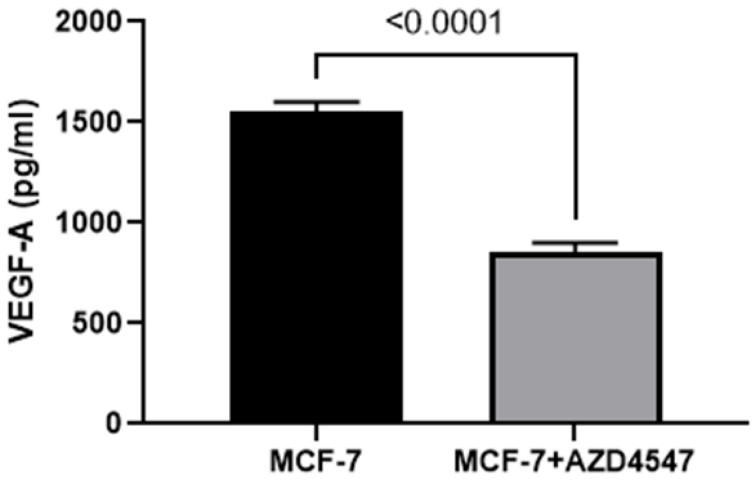

Fig. 4. FGFR1 knockdown inhibits breast cancer angiogenesis via vascular endothelial growth factor-A (VEFG-A) expression.

administration of AZD4547. Data are displayed as mean ± SD (n = 4) and as a percentage of the control (100%, untreated cells). Tukey test and one-way Anova test combined. The treated group proliferation rate was significantly reduced in comparison to the control group, ($p < 0.0001$). After reaching 80% confluency, MCF-7 cells were pricked using a sterile 200 μl pipette tip. By taking pictures of the same location with an inverted microscope outfitted with a digital camera at 0 and 24 hours after scratching, the ability of cells to move into the scratch area was tracked. Results of the migratory image statistically analyzed. The graph displays the average mean ± standard deviation for a minimum of three separate tests, Fig. 3b. The treated group migration rate decreased significantly in comparison to the control group, ($p = 0.0002$). Utilizing the Matrigel Invasion Assay, MCF-7, and MCF-7/AZD4547 cells were evaluated for invasiveness, Fig. 3c. The treated group invasion ability was significantly reduced in comparison to control group, ($p < 0.0001$).

FGFR1 knockdown inhibits breast cancer progression In vivo

In xenograft studies, co-injection of breast cancer cells with FGFR1 knockdown BRCA1 mutant ASCs led to significantly smaller tumor volumes and reduced metastatic dissemination compared to control ASCs. VEGF-A serum level was utilized to reveal decreased angiogenesis and reduced infiltration of inflammatory cells in tumors co-injected with FGFR1 knockdown BRCA1 mutant ASCs, Fig. 4.

After 24 hours of stimulation, VEGF-A in the supernatant was measured using ELISA technique. Every sample was examined three times. 24 hours after stimulation, the amounts of VEGF-A in the supernatant of MCF-7, wild-type, and MCF-7 + AZD4547 cells were measured. VEGF-A in MCF-7 + AZD4547 cells was reduced significantly ($p < 0.0001$) in comparison to MCF-7, wild-type. Every sample was examined three times.

Mechanistic insights immunohistochemical evaluation of NF-κB protein in vitro

FGFR1 knockdown in BRCA1 mutant ASCs significantly downregulated the NF-κB protein signaling pathway as in Fig. 5, which is known to inhibit inflammatory cytokine expression.

As seen in Fig. 5, tumors were treated with AZD4547 for FGFR1 knockdown and with vehicle (control). Tumor treated with a vehicle (control group) Fig. 5a. Tumor AZD4547-treated for FGFR1 knockdown. (x40 magnification) Fig. 5b. Fig. 5c densitometric evaluation of the experimental groups' NF-kB protein expression. The data are displayed in arbitrary units and are expressed as the mean optical density ± standard deviation. The units of data are 2^ (-DDCt). When compared to control, there was a statistically significant difference of ($P = 0.0017$).

Discussion

The role of FGFR1 in breast cancer progression is significant. Studies have shown that FGFR1 amplification and overexpression are associated with poor prognosis in hormonal breast cancer.[20,21]. The upregulation of FGFR1 is linked with elevated mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) activity, which promotes tumor growth and metastasis.[20] In addition, FGFR1 signaling has been implicated in promoting breast cancer

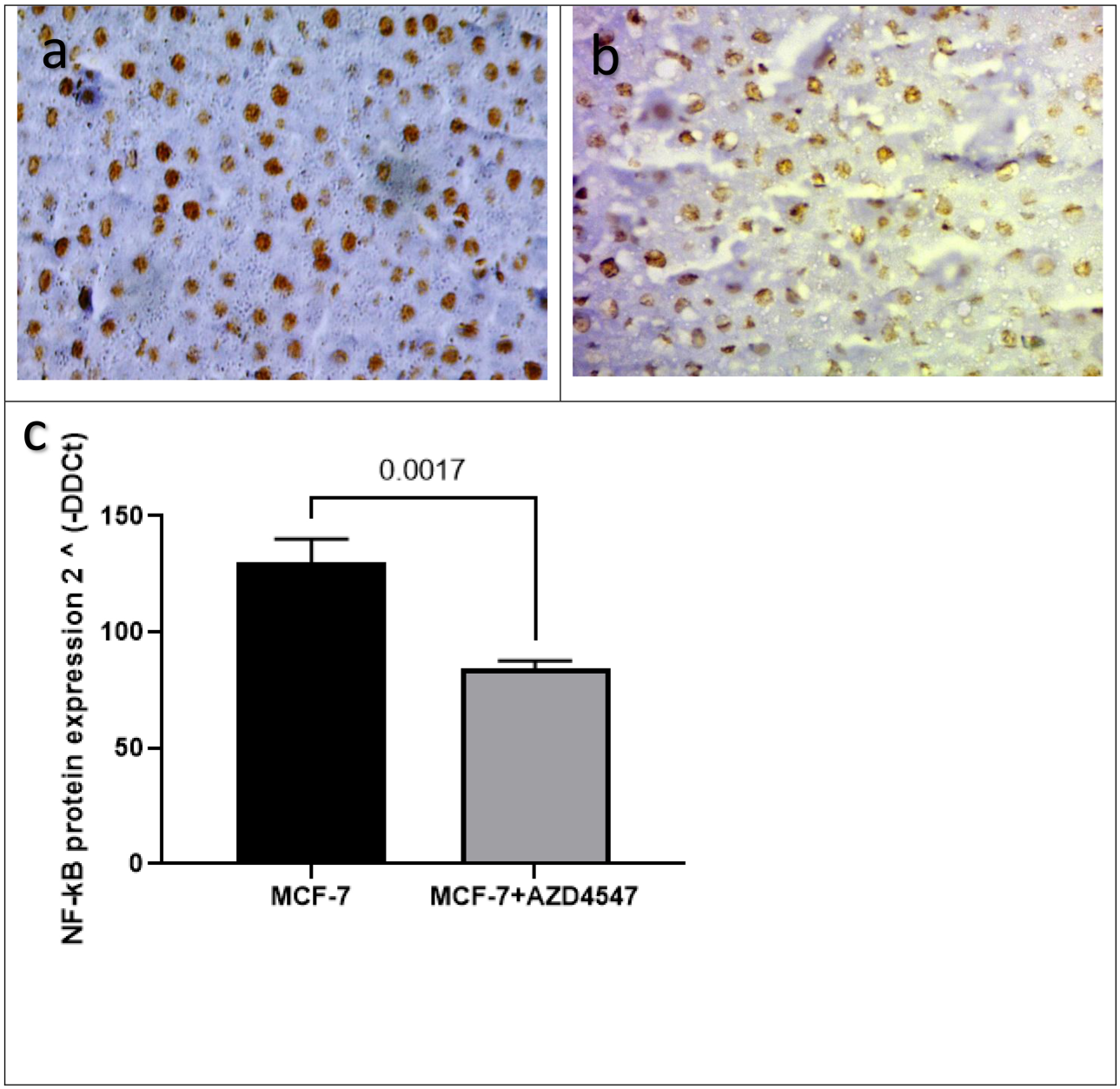

Fig. 5. NF-kB protein immunohistochemistry in breast cancer.

cell metastasis, invasion, and endocrine therapy resistance.[21,22] FGFR1 is significantly overexpressed in invasive carcinoma compared to pure ductal carcinoma in situ (DCIS), suggesting its involvement in the transition to invasive breast cancer.[23] Overall, FGFR1 plays an important role in breast cancer cells proliferation, tumor growth, angiogenesis, and aggressive phenotype, this, emphasizing the importance of FGFR1 as a potential therapeutic target in breast cancer treatment.[24] In this study, we demonstrated the critical role of FGFR1 in BRCA1 mutant ASCs and its contribution to breast cancer progression. Our findings indicate that FGFR1 knockdown in breast cancer has been shown to impact survival in preclinical studies.[13] Thus, our results fit well with previous studies that have suggested that FGFR1 amplification is associated with a worse prognosis and resistance to endocrine therapy in breast cancer,[25] While others have shown that FGFR1 signaling initiates cell division and promotes survival in breast cancer cells, indicating that knockdown of FGFR1 could block these signals, leading to reduced tumor growth and proliferation.[21,26] FGFR1 can also block apoptosis in cancer cells by knocking down

FGFR1, cancer cells become more sensitive to apoptosis, leading to decreased tumor size, burden, and increased rate of survival.[21] Knockdown of FGFR1 is associated with reversal of endocrine resistance in breast cancer cell lines, highlighting its therapeutic potential.[25,27] Furthermore, studies have shown that FGFR1 amplification is higher in invasive carcinoma compared to pure DCIS, suggesting FGFR1 involvement in breast cancer transformation from localized to invasive carcinoma.[28] Overall, FGFR1 knockdown shows a promising approach regarding decreasing breast cancer survival rates and reversing endocrine resistance, thus highlighting its importance as a potential target for breast cancer therapeutic regulations.

Our findings have also shown that knockdown of FGFR1 in BRCA1 mutant ASCs has significantly inhibited pro-inflammatory cytokines IL-6 and TNF-α, which are known to induce cancer cell proliferation, migration, and invasion. Research by Behrer et al., showed that several IL-6 family members are induced by FGFR activation, and that this has helped phosphorylate Signal transducer and activator of transcription 3 (STAT3Tyr 705).[29] To enhance tumor growth and progression, these members also interact with adjacent epithelial cells and cells in the tumor reactive stroma, such as inflammatory cells that infiltrate tumor.[30] Zhang et al., demonstrated that Toll-like receptor 4 (TLR4) and FGFR1 controlled cell migration and proliferation and enhanced the synthesis of pro-inflammatory or immunosuppressive cytokines IL-6 and TNF-α.[31] In addition, Zhao et al., demonstrated that FGFR1 deletion specific to macrophages attenuated High-fat diet (HFD)-induced hepatic inflammation by inhibiting the activation of TNF-α and MAPK signaling pathways and lowering hepatocyte fat accumulation.[32] Therefore, blocking FGFR could result in inhibition of IL-6 and TNF-α levels. Importantly, we found that FGFR1 knockdown in BRCA1 mutant ASCs inhibited breast cancer cells proliferation, migration, and invasion *in vitro*, suggesting a potential therapeutic benefit. A previous study by Yang et al., showed that the activation of iFGFR1 affects the gene expression profile of DCIS-iFGFR1 cells and increases proline-directed kinases (ERK1/2) activity, epithelial-mesenchymal transition (EMT), cell proliferation, tumor growth, and the progression of DCIS to invasive carcinoma.[33] While Chioni et al., showed that FGFR1 cleavage can regulate cancer cells behavior by inhibiting breast cancer cell proliferation, migration, and invasion.[12,34] These findings were confirmed by our *in vivo* xenograft study, where breast cancer cells co-injected with FGFR1 knockdown BRCA1 mutant ASCs significantly reduced tumor growth and metastatic spread, through significant reduction in VEGF levels in mice serums. These findings are consistent with previous studies that have shown that activation of FGFR1 via tumor necrosis factor α-induced protein 3 (TNFAIP3) promotes angiogenesis of breast cancer cells and increases tumor growth through the expression and elevated secretion of VEGFA.[35] While Golfmann et al., showed that tumor angiogenesis was reduced in vivo by FGFR1 deletion in a manner dependent on MAPK.[36] FGFR1 controls the release of proangiogenic VEGF and autocrinally activates the VEGF-VEGFR1 pathway, which in turn increases VEGF secretion through VEGF-VEGFR1-AKT signaling.[37] *In vivo*, targeting both FGFR1 and VEGFR1 had synergistic anti-angiogenic therapeutic effects.[36] Mechanistically, our data recorded that FGFR1 knockdown significantly downregulated the NF-κB signaling pathway, which is a well-established regulator of pro-inflammatory cytokine expression.[38] FGFR1 promotes inflammation through NF-κB signaling in a variety of conditions, particularly in prostate cancer cells and diabetic heart disease.[39,40] Knockdown of FGFR1 has been shown to inhibit NF-κB signaling, emphasizing the importance of FGFR1 in this pathway.[40] Wang et al., have indicated that ectopically produced FGFR1 promotes prostate cancer progression, at least partially, by elevating inflammation in the tumor microenvironment, since inflammation is a major factor in the genesis and advancement of prostate cancer[41] The mechanism by which FGFR regulates the NF-κB pathway is not entirely clear but signaling pathways downstream of FGFR kinase such as extracellular signal-regulated kinases (ERKs), phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT), or phospholipase C γ1 (PLC-γ) are known to activate NF-κB signaling.[42] In addition, Knockdown of FGFR1 to reduce inflammation in the tumor microenvironment of prostate cancer has been demonstrated[43] According to RNA-sequencing research, in hyperglycemic-challenged cardiomyocytes, increased FGFR1 activity triggers pro-inflammatory responses via the MAPKs–NFκB signaling pathway, which further causes fibrosis and hypertrophy.[44] Overall, the research suggests that FGFR1 plays an important role in the promotion of inflammation through NF-κB signaling in disease states, and inhibition of FGFR1 may lead to inhibition of the NF-κB signaling pathway, which may have implications for therapeutic regulations targeting these pathways. Our study highlights the importance of the tumor microenvironment in breast cancer progression, particularly the role of ASCs. Our study focused on BRCA1 mutated ASCs,

which is appropriate given the increased risk of breast cancer associated with BRCA1 mutations. By targeting FGFR1 in these ASCs, we were able to modulate pro-inflammatory cytokine secretion and, subsequently, inhibition of breast cancer progression. Although our findings are promising, further studies are needed to fully elucidate the molecular mechanisms underlying the observed effects and to investigate the potential therapeutic application of FGFR1 inhibition in breast cancer with a BRCA1 mutation. Furthermore, investigating the potential effects of FGFR1 knockdown on other components of the tumor, such as immune cells and endothelial cells, may provide valuable insight into the broader implications of this pathway. This study assumes that the BRCA1 mutated ASC and MCF-7 models are sufficiently representative of the human condition to allow broad conclusions about breast cancer progression and treatment. Modulation of IL-6 and TNF-α by knockdown of FGFR1 is thought to be the main mechanism by which tumor progression is affected. This may facilitate complex interactions among tumor particles. The study also assumes that knockdown of FGFR1 using AZD4547 is effective and specific, without off-target effects that could affect the results. However, there are three study limitations that should be acknowledged. The first limitation is that the research focused on IL-6 and TNF-α as key inflammatory cytokines. While these are important, other cytokines and factors might also play significant roles in cancer progression and could be overlooked. The second limitation is that long-term efficacy and potential side effects of FGFR1 knockdown via AZD4547 were not fully explored in this study, leaving questions about the sustainability and safety of this treatment approach. And finally the study focuses solely on the effects of AZD4547 and does not explore potential synergistic effects with other treatments, which might be relevant for comprehensive cancer therapy.

In summary, our findings demonstrate that FGFR1 knockdown attenuates inflammatory cytokine secretion and inhibits breast cancer progression in BRCA1 mutant ASCs. These results are consistent with previous studies showing that FGFR1 is associated with poor prognosis and treatment resistance in breast cancer.[35,37] However, potential limitations to the present study include focusing only on IL-6 and TNF-α, and the need for further studies to investigate long-term effects and interactions with other therapies.

Conclusion

Our study highlights the importance of targeting the tumor microenvironment, specifically FGFR1, in BRCA1 mutant ASCs as a potential therapeutic strategy for breast cancer treatment via inhibition of inflammatory cytokines secretion and subsequently inhibition of cancer cells proliferation, migration, and invasion, hence prevention gate to metastasis, which may give attention to a promising therapeutic approach to add on breast cancer treatment regulations. Future research should examine the efficacy and long-term efficacy and safety of FGFR1 inhibition in combination with other therapies. Also, warranted for clinical evaluation.

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Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the figures in the manuscript are ours. Furthermore, figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No human studies are present in the manuscript
- The authors have signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee at University of Al-Qadisiyah.

Authors' contribution statement

N. S. S and Z. A. M. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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تثبيط مستقبل عامل نمو الألياف1 FGFR1 عن طريق AZD4547 يثبط تطور سرطان الثدي في الخلايا الجذعية المشتقة من الدهون في متحول BRCA1 عن طريق تعديل الإنترلوكين 6 و عامل نخر الورم ألفا

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الملخص

سرطان الثدي هو مرض معقد ومتعدد الأشكال يطرح تحديات كبيرة في تحديد الاستراتيجيات العلاجية والأهداف العلاجية الجديدة. اظهرت البحوث الحديثة دور الخلايا الجذعية المشتقة من الدهون في تقدم الاورام الصغيرة.تعرف الطفرات في جين سرطان الثدي1 بدورها الاساسي في اصلاح الحمض النووي و تنظيم دورة الخلية, حيث ترتبط بزيادة مخاطر الإصابة بسرطان الثدي والمبيض. كما ظهرت الدراسات أن مستقبل عامل نمو الألياف 1 مرتبط بالعديد من أنواع السرطان، بما في ذلك سرطان الثدي. في الدراسة الحالية، نهدف إلى التحقق من دور مستقبل عامل نمو الألياف1 في خلايا الجذعية السلبية لـ جين سرطان الثدي1 في التجارب المختبرية وفي الجسم الحي وإمكاناتها العلاجية في سرطان الثدي. أظهرت نتائجنا أن تقليل مستقبل عامل نمو الألياف1 قد أوقف بشكل كبير إفراز السيتوكينات المؤيدة للالتهابات، مثل الإنترلوكين-6 وعامل نخر الورم ألفا خلايا الجذعية المتحورة ل جين سرطان الثدي1 كما ادت إلى انخفاض كبير في تكاثر وهجرة وغزو خلايا السرطانية التي تم زراعتها مع خلايا جذعية دهنية تحمل طفرات في جين سرطان الثدي1. اكدت الدراسات الحية لدور مستقبل عامل نمو الألياف1 على تقليل نمو الأورام والانتشار من خلال تثبيط تعبير عامل نمو بطانة الأوعية الدموية وتقليل نشاط مسار عامل نواة كابا. اجمالا تؤكد نتائجنا على اهمية دور الخلايا الجذعية المشتقة من الدهون التي تحمل طفرات في جين سرطان الثدي1 في تقدم سرطان الثدي من خلال تنظيم السيتوكينات الالتهابية. علاوة على ذلك، تشير نتائجنا إلى أن استهداف مستقبل عامل نمو الألياف1 في البيئة الدقيقة للورم، وبشكل خاص في هذه المتحورات قد يكون نهجًا علاجيًا واعدًا في علاج سرطان الثدي. ومع ذلك، هناك حاجة إلى مزيد من الدراسات السريرية.

الكلمات المفتاحية: الخلايا الجذعية المشتقة من الدهون، الطفرات في جين سرطان الثدي1، مستقبل عامل نمو الالياف1، الإنترلوكين 6، السيتوكينات الالتهابية، وعامل نخر الورم ألفا.