Role of annexin A3 in breast cancer (Review)

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Abstract. Annexins are a large group of proteins occurring in numerous cell types. Annexins have roles in events such as coagulation inhibition, endocytosis, exocytosis, signal transduction, proliferation and programmed cell death. The association of annexins with numerous diseases has been reported. There are 12 annexin proteins in total and the association of annexin A3 (ANXA3) with numerous malignant tumor types, such as breast cancer, prostate cancer, lung cancer, stomach cancer and colon cancer, has been reported. Studies investigating the relationship between ANXA3 and breast cancer were analyzed in the present review and it was observed that ANXA3 is expressed at higher levels in breast cancer cells. Furthermore, high ANXA3 levels are a poor prognostic factor, increase the invasion ability of breast cancer cells and may be a novel therapeutic target.

Contents

1. Introduction and background

Annexins are a family of proteins occurring in a variety of cell types (1). They bind calcium and phospholipids to form calcium-dependent ion voltage channels (2). Annexins also have roles in events such as coagulation inhibition, endocytosis, exocytosis, signal transduction, proliferation and programmed cell death, and it has been suggested that calcium binding underlies these effects of annexins (3,4). There are a total of 12 different annexin proteins in mammals. These proteins are named as A1-A11 and A13 (5).

Changes in annexin expression have been demonstrated to be associated with various pathologies, including asthma (6), atherosclerosis (7), autoimmune diseases (8) and Alzheimer's disease (9).

In the present review, the associations of annexin A3 (ANXA3) with breast cancer were investigated. Since there are numerous studies indicating that ANXA3 has a key role in certain cancer types such as breast cancer, the present review focused on this protein.

Associations of ANXA3 with various malignant neoplasms have been reported, including breast cancer (10-19), colorectal cancer (20-23), prostate cancer (24-26), nasopharyngeal carcinoma (27), pancreatic cancer (28), hepatocellular carcinoma (29-33), renal carcinoma (34), thyroid cancer (35), osteosarcoma (36), gastric cancer (37-41) and lung cancer (42-46).

ANXA3, also called placental anticoagulant protein a3 or lipocortin 3, is encoded on 4q13-q22 (6). The ANXA3 molecule has two isoforms with a molecular weight of 36 kDa (containing 323 amino acids) and 33 kDa (containing 284 amino acids) (5,47). Although most neoplasms express only the 36 kDa form, certain cells express both isoforms, or cells such as myeloid cells, prostate adenocarcinoma cells, rat brain cells, may express only one of the two isoforms (33 or 36 kDa) (25,48-50). Le Cabec *et al* (48) reported that both isoforms of 33 and 36 kDa were expressed in myeloblast HL-60 cells. In this study, ANXA3 expression was analyzed by western blot. It was indicated that the expression of the 33 kDA form was higher and that the expression of the 36 kDa form was lower in renal cell carcinoma cells compared to primary cell cultures. This result revealed that both isoforms may have different roles in the carcinogenesis process (47,51). To date, no studies have been performed to differentiate between 36- and 33-kDa ANXA3 by identifying the individual contribution to cancer development and progression.

ANXA has a variable N-terminal region and a fixed C-terminal region. The C-terminal region consists of four or eight annexin repeats. Each of the annexin repeats consists of ~70 amino acids containing phospholipid and Ca^{2+} binding sites (52). The N-terminal region of annexins, which causes different biological activities and functions, consists of 20-200 amino acids (53,54). ANXA3 contains an N-terminus, four additional repeat domains and a C-terminus. Unlike the

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36 kDa isoform, the 33 kDa isoform of ANXA3 does not have the first 39 amino acid residues of the N-terminal region (19). The N-terminus of ANXA3 is involved in the regulation of membrane binding with the tryptophan 5 (W5) domain and non-specific permeability. N-terminal loss or W5 mutation may be observed in the 33-kDA isoform of the ANXA3 molecule. These conditions also alter the membrane interaction by increasing the cellular Ca^{2+} flux (55).

A literature search was performed for the present review via Web of Science, PubMed, MEDLINE and EMBASE to retrieve studies published between January 1, 1990 and January 1, 2022, using the keywords 'annexin A3', 'breast cancer', 'role', 'annexin', 'drug resistance' and 'chemotherapy'. Initially, 14,834 entries were retrieved. Among them, 1,041 studies were open access and available. A total of 1,041 studies were viewed and 888 studies were excluded, as they did not appear relevant to the study subject (based on their titles or abstracts), while 153 studies were retained. Subsequently, 144 studies were excluded for the following reasons: Unsuitable study design (based on their titles or abstracts), duplication, abstract only (the full papers were not accesible), language, insufficient information and other reasons (insufficient number of patients, letters to the editor etc.). Finally, the 9 studies remaining were analyzed in detail and included in the present review. The number of patients in these 9 studies, the method by which the ANXA3 molecule was analyzed, the ANXA3 expression results and the potential roles of this protein are summarized in Table I.

2. Role of ANXA3 in breast cancer development and progression

A previous study suggested that ANCA3 is associated with tumor progression and may be a potential prognostic marker (13). In that study, ANXA3 expression in patients with breast cancer was evaluated by western blot analysis. Furthermore, ANXA3 was inhibited by RNA interference in MDA-MB-231 cancer cells and the effects on proliferation, colonization and invasion were observed. In addition, the ANXA3 levels of 30 patients with breast cancer were evaluated by immunohistochemistry and their association with survival was determined. ANXA3 levels were observed to be higher in MDA-MB-231, HCC-70 and HCC-1954 cells compared to non-cancerous cell lines. It was also observed that ANXA3 silencing suppressed the invasion, wound healing and colonization properties of MDA-MB-231 and HCC-1954 cells. ANXA3 expression was indicated to be closely related to tumor size and high ANXA3 levels were associated with decreased survival rates (13).

In another related study, the mechanisms of the effects of ANXA3 in breast cancer cells were investigated (14). The expression of ANXA3 was observed to be significantly higher in MDA-MB-231 cells than in MCF-7 cells. Following knockdown of ANXA3, which was confirmed by western blot analysis, the percentage of G0/1 cells in the cell cycle and the apoptosis rate were indicated to be significantly higher and the proliferation rate was lower compared with that in the control groups. In the wound healing test, the migratory ability of MDA-MB-231-Sh cells was shown to be significantly lower than that of MDA-MB-231-NC and MDA-MB-231 cells. Furthermore, the cell invasion capacity was lower in MDA-MB-231 cells with ANXA3 knockdown. This study demonstrated that ANXA3 is associated with the proliferation, apoptosis, migration and invasion of breast cancer cells (14).

Li *et al* (17) investigated the roles of ANXA3 in breast cancer *in vivo* in a study using subcutaneous tumors in mice. A total of 18 mice were divided into three groups and inoculated with either native MDA-MB-231 cells, negative control-transfected MDA-MB-231 or MDA-MB-231 cells with ANXA3 knockdown. Flow cytometry was used to evaluate cell proliferation and reverse transcription-quantitative (RT-q)PCR was used to determine ANXA3 mRNA expression. Slower tumor growth was reported for the transfection group. In addition, the tumor weight was observed to be significantly lower in the transfection group ($P<0.01$). ANXA3 levels in the transfection group were indicated to be significantly lower than those in the other groups ($P<0.01$). A lower proliferation index and higher G0/1 population were also observed in the transfection group ($P<0.01$). This study suggested that ANXA3 regulates tumor cell proliferation and growth and may be used as a therapeutic target (17).

3. Effect of ANXA3 on patient prognosis

Zhou *et al* (10) performed a study of 309 patients; higher levels of ANXA3 were detected in cancerous tissue compared to adjacent tissue and ANXA3 levels were reported to be associated with lymphatic metastasis ($P=0.001$) and tumor grade ($P=0.004$). ANXA3 and lymphatic metastases were identified as independent risk factors affecting survival. Higher levels of ANXA3 were detected in cases of triple-negative breast cancer compared to other types ($P<0.002$). No significant difference was observed between groups of different ages, tumor size, stage or menopausal status and ANXA3 levels ($P>0.05$). The results of that study suggested an association between ANXA3 and the progression of breast cancer, which is due to increased lymphatic metastasis. This study also indicated that ANXA3 may be a prognostic marker in breast cancer (10).

In another study, ANXA3 levels were investigated in 60 patients with breast cancer (11). In addition, the effect of RNA interference with ANXA3 on apoptosis of breast cancer cells was investigated. The results suggested that ANXA3 levels were higher in breast cancer compared to normal breast tissues. ANXA3 in carcinoma tissues was also reported to be closely associated with tumor size and axillary metastasis. Kaplan-Meier analysis indicated a significant negative association between high levels of ANXA3 and survival, and ANXA3 overexpression was indicated to be inversely proportional to Bax staining and the apoptosis index. The findings of this study suggested that ANXA3 may be a novel prognostic marker and have a role in the regulation of apoptosis (11).

The clinical implication of ANXA3 in cancer cells vs. normal cells was investigated in a study involving 81 cancer patients. ANXA3 mRNA levels in the samples were determined by RT-qPCR and ANXA3 protein expression was detected by western blot analysis. Proliferation indices were compared between cancer cells and normal cells using flow cytometry. The correlations between gene and protein expression levels of ANXA3 and the proliferation indices of cancer cells were also calculated. ANXA3 levels were observed to

Table I. Details of the 9 papers on the role of ANXA3 in breast cancer included in the present review.

Author, year	Patient number	ANXA analysis method	ANXA3 expression	Potential role of ANXA3	(Refs.)
Kim (2018)	30	Western blot	Increased	Tumour invasion, wound healing, colonization and prognostic marker	(13)
Zhou (2017)	Cell culture (2 cell lines)	Western blot	Increased	Proliferation, apoptosis, migration and invasion	(14)
Li (2018)	18	RT-qPCR	Increased	Tumor cell proliferation, tumour growth and target in therapy	(17)
Zhou (2017b)	309	Immunohistochemistry	Increased	Increased lymphatic metastasis, prognostic marker	(10)
Zeng (2013)	60	Immunohistochemistry	Increased	New prognostic marker, regulation of apoptosis	(11)
Zhou (2018)	81	RT-qPCR, western blot	Increased	Cancer development, metastasis and prognostic marker	(15)
Zeidan (2015)	219	ELISA	Increased	Therapeutic target, migration of neoplastic cells	(12)
Du (2018)	471	Immunohistochemistry	Increased	New therapeutic strategy in the treatment of breast cancer, growth and metastasis of breast cancer	(16)
Zhu (2019)	158	RT-qPCR	Increased	Therapeutic target, prognostic marker	(18)

RT-qPCR, reverse transcription-quantitative PCR; ANXA3, annexin A3.

be significantly higher in breast cancer tissues than in normal cells. It was observed that ANXA3 levels were significantly higher in triple-negative cases compared to luminal A and B types. By contrast, no significant difference in expression levels was observed among other subtypes. It was reported that the proliferation indices of breast cancer cells were significantly higher and were positively correlated with ANXA3. This study revealed that ANXA3 expression may have an important role in cancer development and metastasis and may be an important biomarker in prognosis (15).

4. ANXA3 as a therapeutic target

A study was published that included 219 patients with breast cancer, 192 patients with benign breast pathology and 630 healthy controls (12). The ANXA3 levels of these individuals were determined by mass spectrometry and ELISA. Serum ANXA3 levels were indicated to be significantly higher in patients with benign pathology compared to the other groups ($P<0.0005$). In addition, ANXA3 was determined to be highly expressed in benign and well-differentiated malignant tumour cells. This study demonstrated that ANXA3 is a novel marker in breast tumors, may serve as a therapeutic target and has a role in the migration of neoplastic cells (12).

Du *et al* (16) investigated the relationship of ANXA3 with metastasis and drug resistance in breast cancer. In this study, ANXA3 expression levels were observed to be significantly higher in breast cancer tissues. *In vitro* and *in vivo* analyses indicated that invasion decreased and cell proliferation increased after inhibition of ANXA3. One of the most important contributions of this study was the finding that ANXA3 inhibition increases sensitivity to doxorubicin by increasing drug uptake. Doxorubicin and ANXA3 degradation appeared to suppress tumor growth and metastasis. This study demonstrated the role of ANXA3 in the growth and metastasis of breast cancer and indicated that ANXA3 downregulation may be a novel therapeutic strategy for the treatment of breast cancer (16).

Zhu *et al* (18) investigated the relationship between ANXA3 and chemotherapy efficacy in a study that included 158 patients with breast cancer. A total of 83 patients were treated with epirubicin + cyclophosphamide + 5-fluorouracil (CEF group) and 75 patients were treated with epirubicin + cyclophosphamide + docetaxel (TEC group). Tissue samples were obtained from each patient prior to and 10 days after chemotherapy administration to detect ANXA3 expression, which was determined by RT-qPCR. Significant differences in the rates of remission and progressive disease were reported between the groups ($Z=10.716$, $P=0.013$). The clinical efficacy rate in the TEC group was determined to be significantly higher ($P<0.05$). It was also observed that there was no significant difference between the two groups in terms of bone marrow suppression ($P>0.05$). While there was no difference between the two groups in terms of ANXA3 levels prior to

chemotherapy, ANXA3 levels after chemotherapy were determined to be lower in the TEC group ($P<0.05$). This study revealed that, compared to the CEF regimen, the TEC regimen may improve clinicopathological efficacy, inhibit ANXA3 expression and improve the prognosis of patients (18).

5. Comparison with similar studies

The article published by Yang *et al* (51) is a review reporting the effect of ANXA3 in cancer. However, the present study is only a review article focusing on breast cancer. Therefore, this previous study is more comprehensive; however, it does not include 3 research articles (11,12,18) examined in the present study.

Although the review article by Liu *et al* (19) reporting the effect of ANXA3 in cancer is similar to the present study, the present article is only a review on breast cancer. Furthermore, this previous study does not include 2 research articles (12,18) examined in the present study.

6. Conclusions

To date, numerous studies have been performed with the aim of investigating the relationship between ANXA3 expression and breast cancer. In these studies, the role of ANXA3 in the development, spread, prognosis and treatment processes of breast cancer were investigated. These studies indicated that ANXA3 levels were higher in breast cancer cells than in normal cells, with a significant inverse association between strong ANXA3 expression and survival. Based on the present review, ANXA3 expression is associated with growth, proliferation, apoptosis and invasion of breast cancer cells, and the level of ANXA3 is an important biomarker for the prognosis of breast cancer. Furthermore, ANXA3 is a potential therapeutic target for the treatment of breast cancer. Multicenter studies should be performed with larger patient groups to better understand the roles of ANXA3 in breast cancer and other malignant tumors and develop it as a target and marker for effective treatment programs. These studies will be promising for the treatment and prognosis of breast cancer.

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Authors' contributions

AO was responsible for the conception and design of the review, performed the literature search and selection, wrote the manuscript and edited it. AO read and approved the final manuscript to be published. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

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