Association of ANXA1 and microRNA gene expression with cancer metastasis: A systematic review.

Chaoyang Xu*, Liming Huang, Songxiang Wang*
Department of Breast and Thyroid Surgery, Shaoxing People's Hospital, Shaoxing Hospital of Zhejiang University, Shaoxing, China

Abstract

Metastasis is one of the major obstacles limiting the success treatment of cancer. Annexin A1 (ANXA1) is a key member of the subfamily and belongs to the multi-gene family of annexins, which is known to play an important role in cancer progression and metastasis. Although there were controversies surrounding the relationship between ANXA1 and metastasis, the role of ANXA1 in cancer metastasis has been increasingly recognized. Numerous ANXA1-related signaling pathways are involved in cancer metastasis. Recently through microarray experiments demonstrate that ANXA1 could regulate microRNAs (miRNAs) in cancer, such as miRNA-196a (miR-196a), microRNA-26 (miR-26) and microRNA-562 (miR-562), which promoted cell proliferation and angiogenesis. ANXA1 could regulate miRNAs to directly target NF-κB, estrogen receptor (ER) and angiogenesis gene transcripts. Thus, ANXA1 mediates cancer metastasis may via regulation of miRNA signaling. This review describes the mechanism by which ANXA1 contributes to cancer metastasis and summarizes new advances in research in ANXA1-associated cancer metastasis.

Keywords: Carcinoma, ANXA1, Cancer, Metastasis, miRNA.

Abbreviations:

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Introduction

Metastasis is one of the major causes of death in cancer patients. In particular cancer cell migration and invasion play a crucial role in the progression and metastasis of cancer [1,2]. Thus, a better understanding of the mechanisms underlying these processes is important for the development of novel anticancer agents in order to improve clinical outcome.

ANXA1 is a key member of the subfamily and belongs to the multi-gene family of annexins. ANXA1 protein binds the cellular membrane phospholipids in a Ca$^{2+}$-regulated manner, such as Epidermal Growth Factor Receptor (EGFR), Estrogen Receptor (ER), and Formyl Peptide Receptors (FPR). ANXA1 has been found in several tissues and regulates physiological mechanisms such as cell migration, anti-inflammatory effects, membrane transport, apoptosis and differentiation [7-11].

miRNAs are a group of non-coding RNAs which have been shown to regulate many genes [12]. Recently through microarray experiments demonstrate that ANXA1 could regulate microRNAs (miRNAs) in cancer, such as miRNA-196a (miR-196a), microRNA-26 (miR-26) and microRNA-562 (miR-562), which promoted cell proliferation and angiogenesis [13]. ANXA1 could regulate miRNAs to directly target NF-κB, ER and angiogenesis [14]. This binding interaction results in either mRNA degradation of the gene transcripts or inhibition of translation [14]. Thus, ANXA1 mediates cancer metastasis may via regulation of miRNA signaling.

ANXA1 and Breast Cancer

Breast Cancer (BC) develops through sequential stages from normal ductal epithelium to hyperplasia, ductal carcinoma in situ, invasive cancer, and metastatic carcinoma [15]. In order to improve BC diagnosis and treatment, it is necessary to have a better understanding of etiology. ANXA1 regulates in the mammary gland during the developmental and takes part in intracellular signaling. Several papers indicated that ANXA1 was related to unfavorable prognostic factors in patients with BC [16]. Loss of ANXA1 expression both in DCIS and invasive carcinoma compared to normal epithelium and benign breast diseases in previous studies [16]. Some studies have shown that a higher level of ANXA1 in lymph node metastasis in comparison with primary BC [17,18]. A similar finding was
observed in human breast cancer by a tissue microarray analysis [19].

ANXA1 could regulate miRNAs in breast cancer and it is a target of miRNA-196a (miR-196a), microRNA-26 (miR-26) and microRNA-562 (miR-562) promoted cell proliferation and angiogenesis [13,20,21]. In vivo experiments demonstrate that expression of miR-196a in breast cancer cell induced significantly promotes cell growth [22]. ANXA1 can inhibit the expression of miR-196a, which could stimulation of c-myc and NF-xB expression, regulates BC cell proliferation. ANXA1 could regulate miR-26 and miR-562 directly targeted the NF-xB pathway by targeting the 3’UTR and inhibiting expression of p65 and NF-xB respectively. Overexpression of miR-562 and miR-26 could enhance endothelial tube formation in BC cells.

ANXA1 and Gastric Cancer

Gastric Cancer (GC) remains one of the most common cancers worldwide, and more than one third of GC cases occur in China [23]. However, there are few therapeutic options available for gastric cancer and identification of new biologic targets in patients with GC may contribute to improvement in their outcome.

There has been evidence that inflammation is implicated in GC development [24]. ANXA1 is an endogenous anti-inflammatory protein with a number of biological functions, such as cell migration, inflammation and apoptosis. ANXA1 maybe a poor prognostic factors in patients with GC. Cheng et al. analyze 118 GC patients by immunohistochemical staining [25]. The results show that high ANXA1 expression was associated with more serosal invasion, more peritoneal metastasis, and poorer overall survival in GC patients. A similar finding was observed in gastrointestinal cancer [26].

Accumulated evidences have indicated that ANXA1 subcellular localization are involved in the development, invasion, metastasis and drug resistance of a variety of cancers. There was a study suggestion ANXA1 cytoplasm staining correlation with esophageal and esophagogastric junction adenocarcinoma patient’s survival and loss of ANXA1 expression correlated with gastric cancer patient’s poor outcome [27,28]. Recently study evaluating the prognostic significance of nuclear staining of ANXA1 in oral squamous cell carcinoma patients showed a lower overall survival, whereas decrease of ANXA1 membranous staining in carcinoma do not be involved in oral carcinogenesis [29]. In addition, it has been suggested that ANXA1 nuclear translocation participates in the regulation of cellular proliferation [30,31]. Therefore, it’s suggested that the different subcellular distribution of ANXA1 may also contribute to tumorigenesis and progression in gastric cancer.

In our previous study, we analyzed the correlation of both cytoplasmic and nuclear expression of ANXA1 with different clinicopathological parameters in GC. Nuclear ANXA1 expression was associated significantly with Tumor-Node-Metastasis (pTNM) stage, the nuclear staining of ANXA1 is associated with poor prognosis. And cytoplasmic ANXA1 expression did not correlate with any of pathologic parameters. Our study suggests nuclear localization of ANXA1 correlates with advanced disease stage and peritoneal dissemination in gastric cancer [32]. However, we cannot find any studies about ANXA1 regulate miRNA in GC.

ANXA1 and Other Cancers

Lung Cancer (LC) is the leading cause of cancer-associated mortality worldwide [33]. A previous study demonstrated that ANXA1 expression was significantly higher in patients with Non-Small Cell Lung Cancer (NSCLC), as compared with in control subjects, the similar finding was observed in lung squamous carcinoma cell [34,35]. However, the possible biological function of ANXA1 in NSCLC remains to be elucidated.

ANXA1 is also expression in prostate cancer, and this protein is mainly described to be reduced [36]. In normal prostate tissue ANXA1 expression seems to be confined in basal cells and these latter are extremely rare in Prostate Cancer (PC) mass. The high expression of ANXA1 is maintenance of stem-like in PC cells, which could regulate metastasis by favoring cell migration intracellularly [37].

In esophageal cancer, breast cancer and endometrial cancer, Luthra et al. demonstrated an inverse correlation between ANXA1 mRNA levels and miR-196a in 12 different esophageal, breast and endometrial cancer cell lines and ANXA1 expression could regulation of miR-196a as a marker of esophageal cancer [21].

Conclusion

The past several years have seen significant strides in elucidating the role of ANXA1 in cancer metastasis. Data are starting to accumulate defining ANXA1 mediates cancer metastasis may via regulation of miRNA signaling.

Given this, in the foreseeable future, drug treatment may be guided by individualized genotype databases that can enable personalized drug dosing to enhance therapeutic effect. The past several years have provided mounting evidence for expression of ANXA1 in cancer and ANXA1 expression frequently correlates with cancer metastasis.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Author’s Contributions

Chaoyang Xu-explored the topic, defined the formation and drafted the manuscript, Liming Huang and Songxiang Wang-revised the manuscript and helped its drafting. Zhinong Jiang read and approved the final manuscript.

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Competing Interests
The authors declare that they have no competing interests.

Availability of Data and Materials
Please contact author for data requests.

Consent for Publication
Not applicable.

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*Correspondence to*

Chaoyang Xu

Department of Breast and Thyroid Surgery
Shaoxing People's Hospital
Shaoxing Hospital of Zhejiang University
Shaoxing
China
E-mail: wangsongxian8163.com

Songxiang Wang

Department of Breast and Thyroid Surgery
Shaoxing People's Hospital
Shaoxing Hospital of Zhejiang University
Shaoxing
China
E-mail: xuchaoyangzju.edu.cn