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

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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:

ANXA1: Annexin A1; miRNAs: microRNAs; ER: Estrogen Receptor; EGFR: Epidermal Growth Factor Receptor; FPR: Formyl Peptide Receptors; BC: Breast Cancer; miR-196a: miRNA-196a; miR-26: microRNA-26; miR-562: microRNA-562; GC: Gastric Cancer; LC: Lung Cancer; NSCLC: Non-Small Cell Lung Cancer; PC: Prostate Cancer.

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Introduction

Metastasis is the most common 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-κB expression, regulates BC cell proliferation. *ANXA1* could regulate miR-26 and miR-562 directly targeted the NF-κB pathway by targeting the 3'UTR and inhibiting expression of p65 and NF-κB 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* sub-cellular 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 cancerassociated 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 customized 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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