



Annexin A1 in Malignancy

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Abstract:

Annexin A1 (Anxa1) is an agent of the superfamily of Annexin proteins. Previously, it was known as a mediator in the anti-inflammatory response of glucocorticoids. In several types of research in past decades, it was reported as lipomodulin, lipocortin-1, renocortin, and macrocortin, before it was termed Annexin A1. Anxa1 has complex roles in different essential cellular processes as membrane aggregation, cellular transduction, phagocytosis, inflammation, differentiation, proliferation, and apoptosis. Cumulative evidence has suggested that Anxa1 dysregulations are linked to tumorigenesis, tumor progression, metastasis, invasion, and drug resistance of cancers by contributing to cell proliferation and differentiation, cell apoptosis and signaling. Recently, there is growing evidence indicates that Anxa1 could function either as a tumor promoter or a tumor suppressor candidate for certain cancers relying on the specific type of tumor cells/tissues.

In this article, we attempt to clarify the association between Annexin A1 and malignancies, as well as potential action mechanisms. Anxa1 may serve as prognostic predictor of outcome and response to chemotherapy and a potential target for therapy in the future.

Keywords: Annexin A1; cancer; apoptosis

Introduction

Annexin A1 (Anxa1) is the first agent of the superfamily of Annexin proteins which are phospholipid- and calcium-binding proteins. Anxa1 has been found out in various organisms, including vertebrates, invertebrates, and plants [1].

Anxa1 is an intracellular mediator of glucocorticoids' anti-inflammatory action via phospholipase A2 inhibition [2].

Functionally, Anxa1 has a wide variety of functions in cellular growth, intracellular signaling, and cell differentiation [3]. There is evidence indicated that it participates in the development and consequences of most serious human diseases,

including cancers. Anxa1 levels of expression have been upregulated in some malignant tumors like breast cancer, pancreatic cancer, colorectal cancer, and melanoma. So, Anxa1 could be used as a potential biomarker for tumor progression [4-8]. Conversely, Anxa1 expression levels have been downregulated in other malignancies such as prostate cancer, esophageal-cancer, cholangiocarcinoma and gastric carcinoma [9-12].

The researches in the last decades indicate that Anxa1 could specifically function either as a tumor promoter or suppressor candidate for particular

cancers relying on the specific type of tumor cells/tissues [2].

Annexin A1 (gene name, *ANXA1*) was previously recognized as an intracellular mediator of the anti-inflammatory action of glucocorticoids. In several types of research in the last decades, it was nominated as renocortin lipomodulin, lipocortin-1, and macrocortin, before it was termed Annexin A1 [13]. The superfamily of Annexin proteins has consisted of 13 proteins. Various cell functions, such as inflammation, membrane interactions, cell apoptosis, regulation of proliferation and phagocytosis require Anxa1 to be accomplished [14].

Despite Anxa1 has been found in different types of tumors, the reported Annexin A1 expression levels are conflicting. The high expression level of Anxa1 has been revealed in some malignancies but low expression in others. In consideration of these conflicting data, the mechanism by which Anxa1 contributes to tumorigenesis and tumor progression remains obscure [14].

Structure and biology of Anxa1

The superfamily of Annexin proteins has the same core which consists of 4 homologous repeated domains, approximately 70 amino acids long. Each agent of the superfamily is distinct by having a unique N-terminal region, which is linked to the specific function and biological action of each agent of the superfamily of Annexins [15].

Anxa1 is insensible in plasma while it is detected in many tissues, such as bone marrow, the lung, and intestine [16]. In leucocytes, under resting conditions, Anxa1 is mostly expressed in intracellular granules of eosinophils, neutrophils, and monocytes, with little amounts expressed in some subtypes of lymphocytes [17].

Anxa1 role in carcinogenesis

Deregulation of Anxa1 levels and alterations to its subcellular localization have been linked to the development or even the progression of various types of cancers. High levels of Anxa1 expression have been found in bronchogenic carcinoma [18], hepatoma [19], pancreatic cancer [20], colorectal cancer [21] and in melanomas [22]. A high level of Anxa1 expression is positively correlated with advanced tumor stage and disease severity in these specific forms of cancers.

Also, elevated expression levels of Anxa1 and existence of Anxa1 autoantibodies were found in sera of patients with bronchogenic carcinoma when compared with controls with high risk to develop bronchogenic carcinoma [23], therefore, these findings suggested the potential for Anxa1 to act as an indicator for diagnostic and prognostic purpose in malignancy. Moreover, elevated Anxa1 expression level enhances tumor metastasis and invasion as shown in colorectal cancer while Anxa1 expression levels were elevated in drainage lymph nodes [24]. Conversely, some types of malignancies are more likely to develop in a downregulated expression of Anxa1 including cancers such as cervical [25], oral squamous cell carcinoma [30], lymphoma [26], oesophageal [27], nasopharyngeal [28] and prostate [29]. Interestingly, in oesophageal cancer, Anxa1 levels were higher in well-differentiated tumors in comparison to moderately and poorly differentiated types and levels were lower particularly at the transition from dysplastic to invasive tumors which make Anxa1 an indicator that could act as an early biomarker for progression of tumor [30].

In prostate cancer, Hsiang CH et al (2006) concluded that low Anxa1

expression was associated with prostate acinar morphogenesis due to increased IL-6 suggesting the significance of Anxa1 in mediating cytokine expression. Restoring Anxa1 expression in prostate cancer cells reduces cellular viability and induces a proapoptotic effect via activation of JNK and p38 pathways and blockage of EGF-mediated proliferation [31].

Anxa1 Signal Pathway Involved in Cancer

Signaling Pathways in the proliferation process

Anxa1 is involved in the inhibition of cellular proliferation through the signal transduction (ERK/MAPK pathway). The ERK/MAPK pathway, which is involved in tumor development and progression, is activated by upregulated Anxa1 and potentiates the inhibition of tumor proliferation. Activated ERK/MAPK by Anxa1 leads to the collapse of the actin skeleton and downregulation of cyclin D1 expression [32]. Interleukin 6 (IL-6) expression was found that it is negatively correlated to Anxa1 expression and low Anxa1 expression was reported, by Cicek M et al (2004), to promote the development of prostate cancer and enhance tumor aggressiveness by increasing IL-6 activity and expression [33]. A previous study concluded that Anxa1 is an essential cellular protein using mass spectrometry analysis and two-dimensional proteomic of metastatic human breast cell lines (MDA-MB-435 cells), but are downregulated in metastasis-suppressed BRMS1-transfected MDA-MB-435 cells. Moreover, both of them mediated tumor metastasis suppression through BRMS1 [34]. The aforementioned signaling pathways involve cancer cell proliferation. The upregulation of Anxa1 inhibits the proliferation of cancer cells, whereas the

downregulation of Anxa1 enhances cell proliferation [14].

Signaling Pathways in apoptosis

The inhibitor of histone deacetylase FR235222 (now called LGP1) increases Anxa1 expression at the level of transcription. Moreover, LGP1 promotes cell apoptosis in cancer prostate through a caspase pathway. In contrast, low Anxa1 expression suppresses LGP1-induced apoptosis, which indicates that Anxa1 has a pro-apoptotic effect and that it regulates apoptosis [35].

Anxa1 contributes to signal transduction and activation of p38 and JNK during proliferation and apoptosis. Reintroduction of Anxa1 activates p38 and JNK and initiate apoptosis [31]. As another mechanism, cytosolic phospholipase A2 (cPLA2) which is inhibited by Anxa1 could be activated by tumor necrosis factor (TNF). Dexamethasone increases the synthesis of Anxa1 and enhances the resistance of U937 leukemic cells to apoptosis through TNF pathway. These signaling pathways involve the apoptosis of malignant cells [14].

Anxa1 in Hematological Malignancies

Anxa1 in Lymphoma

Anxa1 is associated with B-cell lymphomas. Loss of *ANXA1* potentially participates in B-cell lymphoma development. Compared with the positive expressions of Anxa1 mRNA and protein in normal B cells, *ANXA1* was commonly lost in B-cell lymphoma tissues [36]. Gene deletion was not the cause for *ANXA1* loss as Southern blot analysis indicated that the *ANXA1* gene was normal in B-cell lymphoma Raji and OMA-BL-1 cells. Indeed, the methylation of the *ANXA1* promoter may be a possible mechanism for its silencing, as the expression of *ANXA1* in B-cell lymphomas restored when exposed to a demethylation agent (methylase inhibitor deoxycytidine) [36].

ANXA1 may be a candidate resistance gene for T-cell lymphomas. Following γ -irradiation, its expression level was significantly decreased in thymus stroma cells of T-cell lymphoma [37]. Interestingly, *ANXA1* levels in T-cell lymphoma-resistant SEG/Pas mice (nested recombinant haplotypes 1 [NRH1]) was statistically higher than T-cell lymphoma-sensitive C57BL/6J mice following γ -irradiation [38].

Anxa1 in hairy cell leukemia

Anxa1 protein was upregulated in Hairy cell leukemia (HCL). However, it was not associated with other B-cell lymphomas [39]. Falini et al, (2004) reported that Anxa1 has high sensitivity for HCL and 100% specificity. Anxa1 could be a potential diagnostic marker of HCL, specifically distinguishing it from other B-cell lymphomas [40].

Anxa1 in acute myeloid leukemia

Few studies were designed to investigate Anxa1 in acute myeloid leukemia. López-Pedrerá et al. (2006), aiming to study the pattern of expression of different proteins including Anxa1 expression in blast cells from AML patients in comparison to healthy controls, declared that Anxa1 is significantly overexpressed in AML BM blasts when compared to control subjects in a study of a total of 13 AML patients versus 10 healthy controls [41]. Sabran et al. (2019) as well, found in an experimental study on AML cell line (U937) that Anxa1 had a significantly higher concentration compared to the mononuclear cells of peripheral blood obtained from healthy donors [42]. On the basis of a proteomic study, Kaźmierczak et al. (2013) reported that analysis of blood and bone marrow samples obtained from AML patients before induction therapy, they found 4 proteins, including Anxa1 that significantly correlated with results of treatment. Anxa1 expression level was

present in both subgroups (patients who achieved CR and patients who did not), however, its concentrations were significantly higher in the subgroup with CR [43].

Methods of assessment:

Many laboratory methods are used to detect Annexin A1 protein as immunocytochemical assay in hairy cell leukemia [40], flow cytometry method using bone marrow samples in AML and immunophenotyping method using tissue sample in hepatocellular carcinoma [44]. Also, Western Blotting and Immunofluorescence assay were used in detection of Annexin A1 in pancreatic carcinoma [45].

Conclusion

Anxa1 is a potential indicator of diagnostic, therapeutic, and prognostic purposes of certain malignancies. More researches are required to investigate the detailed mechanisms of Anxa1 in tumors.

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