

Association of annexin A2 with cancer development (Review)

XIAO-HENG XU¹, WEI PAN², LI-HUA KANG¹, HUI FENG¹ and YAN-QIU SONG¹

¹Cancer Center, The First Hospital of Jilin University, Changchun, Jilin;

²Department of Pediatrics, The Second Hospital of Jilin University, Changchun, Jilin, P.R. China

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Abstract. Annexin A2 (ANXA2) is a well-known calcium-dependent phospholipid binding protein widely distributed in the nucleus, cytoplasm and extracellular surface of various eukaryotic cells. It has been recognized as a pleiotropic protein affecting a wide range of molecular and cellular processes. Dysregulation and abnormal expression of ANXA2 are linked to a large number of prevalent diseases, including autoimmune and neurodegenerative disease, antiphospholipid syndrome, inflammation, diabetes mellitus and a series of cancers. Accumulating data suggest that ANXA2 is aberrantly expressed in a wide spectrum of cancers, and exerts profound effects on tumor cell adhesion, proliferation, apoptosis, invasion and metastasis as well as tumor neovascularization via different modes of action. However, despite significant research, our knowledge of the mechanism by which ANXA2 participates in cancer development remains fragmented. The present review systematically summarizes the effects of ANXA2 on tumor progression, in an attempt to gain an improved understanding of the underlying mechanisms and to provide a potential effective target for cancer therapy.

Contents

1. Introduction
2. Properties of annexin A2

Correspondence to: Dr Yan-Qiu Song, Cancer Center, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, Jilin 130021, P.R. China
E-mail: songyanqiu1957@hotmail.com

Abbreviations: tPA, tissue plasminogen activator; ECM, extracellular matrix; NES, nuclear export signal; STAT6, signal transducer and activator of transcription 6; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial cell growth factor; bFGF, basic fibroblast growth factor; EC, endothelial cell; MMPs, matrix metalloproteinases; VE-cad, vascular endothelial cadherin; EPCs, endothelial progenitor cells

Key words: cancer, annexin A2, adhesion, proliferation, neovascularization, invasion and metastasis

3. Aberrant expression of annexin A2 in cancers
4. Annexin A2 and tumor cell adhesion
5. Annexin A2 and tumor cell proliferation
6. Annexin A2 in tumor neovascularization
7. Annexin A2 in tumor invasion and metastasis
8. Conclusion

1. Introduction

Cancer remains a major public health issue due to the limitations of current therapy. Despite improvements in surgical techniques, radiation therapy and chemotherapy, there has been no major improvement in the effective blockage of tumor progression. Tumor development is a complex stepwise process involving the accumulation of abnormalities in miscellaneous molecules that drive tumor growth and progression by coordinating critical interactions between tumor cells and the host microenvironment, including a variety of normal stromal cell types, the extracellular matrix (ECM), proteases and cytokines (1). Thus, an improvement in the prognosis of cancer will require the successful development of more effective molecular-targeted therapies. Annexin A2 (ANXA2) is one of the most important molecules that are aberrantly expressed in a wide range of cancers and participate in tumor cell adhesion, proliferation, invasion, metastasis and tumor neovascularization, thereby playing a crucial role in cancer growth and progression (2-4). In this review, we summarize the contribution of ANXA2 to cancer development and the underlying mechanisms, in an attempt to highlight the effects of ANXA2 on tumor cell adhesion, proliferation, invasion, metastasis and tumor neovascularization, and to provide a therapeutic target for molecular-based strategies.

2. Properties of annexin A2

ANXA2 (also called p36, calpactin I heavy chain and lipocortin II) is a 36-kDa protein belonging to the calcium-dependent phospholipid binding proteins (5-7). It is structurally highly conserved and is expressed in nearly all eukaryotes (7-10), where ANXA2 is distributed mainly in the plasma membrane (11) and cytoplasm with a small proportion in the nucleus (12). Similar to other annexins, the basic structure of ANXA2 consists of a homologous C-terminal core composed of four repeats, and a highly variable N-terminal tail (13,14). The C-terminus of ANXA2 harbors the binding sites of

calcium, phospholipids and F-actin which are necessary for the membrane-associated activities of ANXA2 (15-21). This domain also interacts directly with various molecules such as heparin and RNA, thus endowing ANXA2 with more regulating actions (22-25). The N-terminal domain of ANXA2 contains a nuclear export signal (NES) (12) as well as multiple phosphorylation sites such as Tyr23, Ser11 and Ser25, which can be phosphorylated by Src kinase and protein kinase C, respectively (26-28). The phosphorylation of ANXA2 affects its intracellular localization and regulating actions in specific cell types (29-38). Moreover, ANXA2 has been identified as a cellular redox regulatory protein, and this action is related to a reactive cysteine residue (Cys-8) in the N-terminus. These domains dictate its functional and regulatory specificity distinct from other annexin members (39).

ANXA2 exists as a monomer or as a heterotetramer (AIIIt). AIIIt consists of 2 molecules of ANXA2 and a dimer of S100A10 (P11), and possesses a spectrum of biological behavior (40-42). The most well-documented function of ANXA2 is the interaction with tissue plasminogen activator (tPA) as well as its substrate, plasminogen, and promotes the conversion of plasminogen into plasmin (10,42-44) by which it regulates the fibrinolytic process (45), facilitates tissue remodeling, degrades ECM and participates in angiogenesis (46-48) when it locates on the extracellular surface. The expression of ANXA2 in the cytoplasm and plasma membrane is involved in the regulation of actin cytoskeleton dynamics (6,19,21,49), endocytosis and exocytosis (31,50-52), cell-cell adhesion (5,53,54), cell polarity (55) and endosome formation (56,57). ANXA2 has also been shown to play an important role in DNA synthesis and mRNA transport and translation after identification of a small population existing in the nucleus and a NES in the N-terminus of this protein that regulates its nuclear export (12,58). ANXA2 acting as a part of the primer recognition protein complex and as a DNA-binding protein regulates DNA polymerase α activity, DNA synthesis, cell proliferation and cell cycle progression (59-66). Other studies have revealed that ANXA2 directly binds to ribonucleotide homopolymers, cytoskeleton-bound polysomes and is involved in association of mRNA with the cytoskeleton and perinuclear localization (25). The nuclear accumulation of the ANXA2 monomer plays a role in protecting the cells from DNA damage during oxidative stress (67). More recently, increasing data have shown that ANXA2 is implicated in a wide range of biological action such as facilitating the cell cycle partly through a p53-dependent mechanism (68), regulating signal transducer and activator of transcription 6 (STAT6) activity (69) and participating in multiple redox cycles (39). Post-translation modification of ANXA2 such as acetylation and phosphorylation regulates its localization, NES, as well as binding to S100A10 and plasminogen, which determines its biological activation (29,31-35,37,38). Phosphorylation of ANXA2, at Tyr23 for example, was found to induce actin reorganization and cell scattering in MDCK cells (30); meanwhile, Tyr23 phosphorylation is required for cell-surface localization of ANXA2 involved in pancreatic ductal adenocarcinoma invasion (36). ANXA2 is aberrantly expressed in a wide spectrum of tumors, and this abnormal expression of ANXA2 plays a crucial role in tumor growth and progression.

3. Aberrant expression of annexin A2 in cancers

ANXA2 is one of the most common proteins that are over-expressed in a series of cancers and are implicated in the multistep processes of tumor development. The first association between ANXA2 and tumorigenesis was described in hepatocellular carcinoma (HCC) in 1990, in which an abundance of ANXA2 was detected (70). Recently, a number of studies have found the increased expression of ANXA2 at both the protein and mRNA levels in many types of malignancies such as colorectal (71,72), breast (73-76) and lung cancer (77), HCC (78), gastric carcinoma (79) and pancreatic cancer (80), particularly in the more aggressive or poorer prognosis phenotype of these cancers (81-84). As a secretory protein, the serum level of ANXA2 was also found to be elevated in patients with cancers, including HCC (78,85,86) and invasive breast cancer (87).

There is increasing evidence to suggest that overexpression of ANXA2 is closely associated with the differentiation status, histological type, lymph node metastasis and distant metastasis in non-small cell lung cancer (NSCLC) (68,88,89), colorectal (71,90,91) and gastric cancer (79,84). Statistical analysis has also shown that ANXA2 overexpression is correlated with a reduced survival time and a higher risk of recurrence in colorectal (71), pancreatic (80,92), gastric (79), clear-cell renal cell carcinoma (83) as well as NSCLC (88,89). These studies indicate the involvement of ANXA2 in tumor progression. In contrast, ANXA2 was also found to have an inverse correlation with esophageal carcinomas (93,94) as well as head and neck squamous cell carcinoma (95). In other words, the expression of ANXA2 was found to be significantly lower in tumor tissues compared to its paired adjacent normal tissues in these cancers, and the downregulation of ANXA2 was significantly correlated with advanced clinical stage, more frequent recurrence and regional lymph node and distant metastasis. The different experimental techniques and the difference between primary tumors and metastatic lesions may be responsible for these contradictory findings.

Taken together, these data indicate that aberrant expression of ANXA2 is an important prognostic factor in a number of tumor types, and exerts profound effects on tumor progression.

4. Annexin A2 and tumor cell adhesion

High ANXA2 expression in cancer cells and tumor stroma has been implicated in tumor cell adhesion. Initial evidence for the involvement of ANXA2 in tumor adhesion was discovered in RAW117 large cell lymphoma cells (96). This study demonstrated that the binding of RAW117 tumor cells to endothelial cells (ECs) was mediated by ANXA2 expressed on the surface of the RAW117 tumor cells, and this binding was inhibited by antibodies of ANXA2, indicating the association of ANXA2 with tumor cell adhesion. In the secretome of co-cultured cells, ANXA2 siRNA significantly inhibited ovarian cancer cell adhesion to peritoneal cells, supporting the role of ANXA2 in cell adhesion (97). Similarly, the ability of prostate cancer PC-3 cells to bind to human bone marrow ECs and osteoblasts was significantly blocked by an antibody to ANXA2 or the N-terminal competing peptide of this protein. The adhesive capacity of PC-3 cells to osteoblasts

derived from *Anxa2*^{+/+} mice was significantly increased compared to those from *Anxa2*^{-/-} mice, further supporting the involvement of ANXA2 in tumor adhesion (98). However, the underlying mechanism responsible for the actions of ANXA2 in tumor adhesion remains unclear. Recently studies have demonstrated that the adhesion between breast cancer cells and ECs is mediated by interactions between ANXA2 and S100A10. ANXA2 expressed on the surface of breast cancer cells interacts with S100A10 located on microvascular ECs, facilitating the process by which cancer cells form cell-cell contact with microvascular ECs (99).

5. Annexin A2 and tumor cell proliferation

ANXA2 is a key contributor to the stimulation of tumor cell proliferation and promotion of cancer growth under multiple regulatory modes. A relatively early study demonstrated a higher expression of ANXA2 in pancreatic carcinoma cell lines compared with cells of the normal pancreas, and an inverse relationship was noted between the levels of ANXA2 and the doubling time of the culture cells (100). As one of the most highly expressed genes in primary multiple myeloma (MM) cells (101), ANXA2 was found to increase cell proliferation and inhibit cell apoptosis (2). Downregulation of ANXA2 expression by siRNA in lung cancer A549 cells or breast cancer MDA-MB-231 and JIMT-1 cells significantly decreased the cell proliferative capacity (74,102). Similarly, in human HCC cells, silencing of ANXA2 suppressed cell proliferation and led to abnormal apoptosis, and the percentage of cells in the S phase was markedly decreased (103). When ANXA2 was suppressed by RNA interference (RNAi) in breast cancer cells, the treated cells were found to accumulate in the G0/G1 phase accompanied by a decrease in the S/G2+M phase population and a reduction in cell proliferation (104). ANXA2 facilitates proliferation and inhibits apoptosis via different pathways in a wide range of cancer cell types. ANXA2 was suggested as a part of the primer recognition protein complex and DNA binding protein involved in DNA replication (61,62,64,65). ANXA2 was also identified as an RNA-binding protein interacting with specific mRNAs such as its cognate mRNA and c-myc mRNA that are involved in the transport and/or anchorage of specific mRNAs (25,105-107). In human HeLa, 293 and 293T cells, for example, downregulation of ANXA2 protein levels reduced DNA synthesis and inhibited cell division and proliferation (66). The interaction of ANXA2 and c-myc mRNA was found to lead to the increased expression levels of c-myc protein which is involved in cell proliferation, differentiation and apoptosis (108). It is well known that p53, as a tumor suppressor, plays a critical role in cell cycle regulation and apoptosis in different cancer cells. ANXA2 has also been proposed to be involved in p53-mediated apoptosis based on a study that overexpression of p53 induced apoptosis of lung cancer cells concomitantly with downregulation of ANXA2. In addition, ANXA2 knockdown increased the levels of p53 and its downstream gene expression, and caused p53 translocation from the cytoplasm to the nucleus (109). *In vivo* and *in vitro* studies showed that ANXA2 facilitates cell cycle progression and cell proliferation in part mediated by inhibition of p53 expression (68). Furthermore, ANXA2 was reported as a receptor mediating proliferative and anti-

apoptotic effects of progastrin/gastrin on target cells such as colon cancer and pancreatic cancer (110,111).

6. Annexin A2 in tumor neovascularization

A considerable body of research has documented that angiogenesis is one hallmark of cancer (112), and is required for tumor growth, migration and metastasis (113,114). This process is initiated by the activation of proangiogenic factors such as vascular EC growth factor (VEGF), basic fibroblast growth factor (bFGF), plasminogen, followed by degradation of the ECM and proliferation and migration of ECs, as well as the synthesis of new matrix components (115-118). Increased ANXA2 expression in tumors has been recognized as a key contributor to cancer angiogenesis *in vivo* and *in vitro* (47,119). Studies in human breast tumor xenograft models have demonstrated that neoangiogenesis in the tumor microenvironment can be markedly inhibited by the ANXA2 antibody, indicating the involvement of ANXA2 in new vessel formation in cancer (120). Clinical specimens also showed that the accumulation of tPA and ANXA2 on the surface of invasive human breast cancer was correlated with tumor neovascularization (48). The plasminogen/plasmin system activated matrix metalloproteinases (MMPs) into active protease which is required for the degradation of the ECM during the sprouting of new blood vessels (121). ANXA2 plays an important role in the plasminogen activation system and acts as a tPA receptor on the cell surface of endothelial and cancer cells, which mediates the conversion of plasminogen into plasmin (44,48). In addition, ANXA2 also participates in VEGF-mediated neovascularization. ANXA2 was found to be increased in a murine model of ischemic retinopathy through a VEGF/VEGF-R2/PKC β pathway (122). Silencing of the ANXA2 gene by siRNA inhibited the expression of proangiogenic molecules, including VEGF, leading to the inhibition of neovascularization (2). Simultaneously, addition of purified domains I and IV of ANXA2 partly inhibited VEGF-dependent formation of capillary-like networks in a dose-dependent manner (123). Furthermore, ANXA2 was demonstrated to interact directly with the vascular endothelial cadherin (VE-cad)-based complex which is required to maintain VE-cad-dependent cell-cell junctions responsible for the maintenance of vascular endothelium integrity (124). The domains I and IV of ANXA2 compete with endogenous ANXA2 for interaction with VE-cad, leading to the disruption of the capillary-like network by affecting endothelial cell-cell contacts (123). Studies also showed that under the stimulation of sphingosine 1 and angiogenic growth factors, ANXA2 regulated Akt activation in sprouting angiogenesis, and depletion of ANXA2 attenuated Akt activation during EC invasion which was associated with increased phosphorylation of VE-cad and endothelial barrier leakage (125).

Importantly, increased vasculogenesis which occurs via mature ECs from proliferation and differentiation of bone marrow-derived endothelial progenitor cells (EPCs) has been recognized to contribute to tumor development (126-128). In addition to the direct cellular contribution to new vessel formation, EPCs secrete a spectrum of proangiogenic cytokines that promote not only angiogenesis but vasculogenesis by different modes, thus playing a crucial role in neovascularization

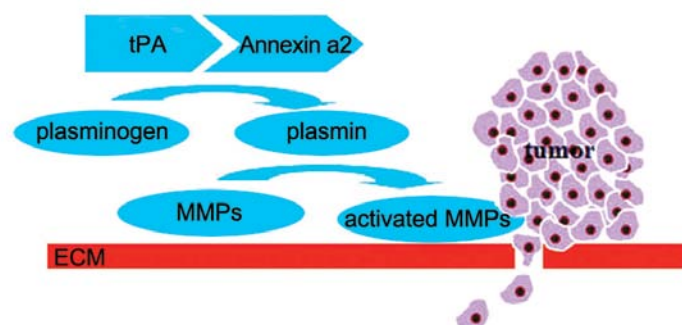


Figure 1. Annexin A2 facilitates tumor invasion and metastasis. Annexin A2 catalyzes the conversion of inactive enzyme plasminogen into the active serine protease plasmin via the interaction with tPA. Plasmin activates MMPs which cause ECM degradation, leading to tumor cell invasion and metastasis. tPA, tissue plasminogen activator; MMPs, matrix metalloproteinases; ECM, extracellular matrix.

during neonatal growth and tumor progression (126-128). However, EPCs mobilized from the bone marrow into the peripheral circulation, migrating and adhering to the sites of new vessel formation is a complex process dependent on cell active mobility. Cytoskeleton remodeling plays crucial roles in cell mobility. Various cell activities, including migration, morphological change and polarity formation are regulated by actin filament dynamics, including actin filament disassembly, severing and reorganization (129,130). Studies have shown that the dysfunction of actin leads to the impairment in EPC functions, including tube formation (131,132). ANXA2 plays a crucial role in regulating actin cytoskeletal rearrangements by binding the regions of free-barbed ends (19). Thus, ANXA2 may be involved in the neovascularization of EPCs by interacting with actin, yet this theory requires more supporting evidence.

These findings indicate that ANXA2 plays a crucial role in tumor progression by enhancing neovascularization. Thus, ANXA2 may be a potential target for the therapeutic management of cancer via blockage of ANXA2-mediated neovascularization.

7. Annexin A2 in tumor invasion and metastasis

Tumor invasion and metastasis is responsible for the majority of deaths among cancer patients. This complex process includes adhesion of tumor cells to ECM proteins, proteolysis of ECM proteins and remodeling of ECM. Through these mechanisms, tumor cells create intercellular spaces for migration, an event that requires membrane synthesis and cytoskeletal rearrangements. The contribution of ANXA2 to tumor invasion and metastasis by interacting with its potential invasion-associated protease proteins as well as the actin cytoskeleton has been reported in many advanced human tumors. In breast cancer, for example, ANXA2 was found to be overexpressed in the highly invasive cell line MDA-MB-231 compared with a poorly invasive cell line MCF-7 (75). In MCF-7/ADR cells, the administration of adriamycin increased the expression of ANXA2 consistent with the enhancement in cell proliferation and invasion, suggesting the involvement of ANXA2 in cancer cell invasion (133). In two head and neck squamous cell carcinoma cell lines, respectively, ANXA2 was found to be upregulated in metastatic lymph node compare with the primary tumor of the same patient (134).

Analogously, the elevated expression of ANXA2 was also detected in lymph node metastatic tissues of lung cancers (88). ANXA2 was also differentially expressed in a pair of canine glioma subclones that exhibited different invasive phenotypes in rat brains yet had similar genetic backgrounds (135). In addition, the reduction in ANXA2 expression by siRNA or neutralizing antibodies significantly inhibited the motility and invasion of a number of cancer types such as ovarian cancer, human glioma and HCC (97,103,136), further supporting the contribution of ANXA2 in tumor invasion. Accumulating data suggest that the plasminogen activation system plays a crucial role in various processes of tumor development, including activation of MMPs, degradation of ECM and switch of growth factors, which together facilitate cellular migration and invasion (137-142). The conversion of inactive enzyme plasminogen to active serine protease plasmin is a key event in this process, which is mediated by plasminogen activators, t-PA and urokinase plasminogen activator (uPA). ANXA2 catalyzes the conversion via the interaction with tPA, thus efficiently enforcing the effects of plasmin on tumor angiogenesis and tissue remodeling, MMPs and latent growth factor activation, and ECM degradation, leading to tumor progression and metastasis (44,45,143) (Fig. 1).

Moreover, ANXA2 has also been shown to regulate migration and invasion of tumor cells by interaction with other proteins. In invasive human breast cancer cell lines which over-express ANXA2, the invasive capacity of the cancer cells was decreased by the siRNA of ANXA2 via inhibition of c-myc expression (104). In contrast, upregulation of ANXA2 in the noninvasive breast cancer cell line MCF-7 was correlated with enhanced migration and invasion ability of cells both *in vitro* and *in vivo* by increasing expression of c-myc and cyclin D1 via activation of the Erk1/2 signaling pathways (144). In HCC, the interaction between ANXA2 and CD147 was found to regulate the trafficking of CD147-harboring membrane microvesicles thereby promoting the production of MMP-2 by tumor stroma fibroblasts, and suppressing the migration and invasion of tumor cells (145,146). ANXA2 was also confirmed to promote pancreatic cancer cell motility by interaction with S100A6 (147). Studies also showed that the location of ANXA2 on the cell surface promoted TGF β -Rho-mediated epithelial-mesenchymal transition (EMT) in pancreatic ductal adenocarcinoma (36) which is an important process for the invasion and metastasis of this cancer (148).

These results indicate that ANXA2 may be a vital component in the regulation of tumor invasion and metastasis, and understanding of the mechanisms of ANXA2-mediated tumor development is crucial.

8. Conclusion

Development of a tumor involves a complex process, and multiple pathological events are considered to mediate and drive tumor cell growth and development. ANXA2 is an important molecule involved in regulating tumor cell adhesion, proliferation, invasion, metastasis and tumor neovasculogenesis, thus playing a crucial role in tumor development. The cellular and molecular mechanisms of the effects of ANXA2 on tumor development require further elucidation, and may provide a potential efficient therapeutic target for molecular-based strategies for tumor treatment.

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