Review Article

Annexin A1 affects tumor metastasis through epithelial-mesenchymal transition: a narrative review

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Background and Objective: Annexin A1 (annexin I, ANXA1), the first discovered member of the annexin superfamily, plays important roles in tumor development, invasion, metastasis, apoptosis and drug resistance based on tumor type-specific patterns of expression. The acquisition of the epithelial-mesenchymal transition (EMT) characteristics is an essential mechanism of metastasis because they increase the mobility and invasiveness of cancer cells. Cancer invasion and metastasis remain major health problems worldwide. Elucidating the role and mechanism of ANXA1 in the occurrence of EMT will help advance the development of novel therapeutic strategies. Hence, this review aims to attract everyone's attention to the important role of ANXA1 in tumors and provide new ideas for clinical tumor treatment.

Methods: The PubMed database was mainly used to search for various English research papers and reviews related to the role of ANXA1 in tumors and EMT published from November 1994 to April 2022. The search terms used mainly include ANXA1, EMT, tumor, cancer, carcinoma, and mechanism.

Key Content and Findings: This article mainly provides a summary of the roles of ANXA1 and EMT in tumor metastasis as well as the various mechanisms via which ANXA1 facilitates the occurrence of EMT, thereby affecting tumor metastasis. In addition, the expression of ANXA1 in different metastatic tumor cell lines and its roles in tumorigenesis and development are also elaborated. This article has found many tumorous therapeutic targets related to ANXA1 and EMT, further confirming that ANXA1 has a huge potential for the diagnosis, treatment and prognosis of certain cancers.

Conclusions: Both the abnormal expression of ANXA1 and the occurrence of EMT are closely related to the invasion and metastasis of tumors, and more interestingly, ANXA1 can impact EMT directly or indirectly by mediating signaling pathways and adhesion among cells. We need more studies to elucidate the effects of ANXA1 on tumor invasion, migration and metastasis through EMT *in vitro* and *in vivo* clearly, and ultimately in patients to identify more therapeutic targets.

Keywords: Annexin A1; epithelial-mesenchymal transition (EMT); tumor metastasis; molecular mechanism

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Introduction

There have been many reviews on the role of Annexin A1 (annexin I, ANXA1) in different tumors and the occurrence, development and mechanism of EMT in tumors. ANXA1, a calcium-dependent phospholipid-binding protein, is widely expressed in various bodily tissues and cells and exerts wide-ranging biological effects on processes such as inflammatory regulation, cell signal transduction, cell proliferation, differentiation and apoptosis (1). Increasing evidence supports that the dysregulation of ANXA1 plays an important role in the occurrence of the epithelial-mesenchymal transition (EMT) and may affect the metastasis of various tumors, and the relationship between ANXA1 and EMT is thus worthy of further study.

However, there is no report that summarizes the relationship between ANXA1 and EMT and how ANXA1 affects tumor invasion and metastasis through EMT. Therefore, in this review, we not only describe the role of ANXA1 in the occurrence and development of certain cancers but also summarize the various mechanisms by which ANXA1 acts on EMT and affects tumor metastasis. ANXA1 has potential as a biomarker for the diagnosis, treatment and prognosis of certain cancers. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1544/rc).

Methods

Information used to write this paper was collected from the sources listed in *Table 1*.

ANXA1

The Annexin family

Annexins are a superfamily of calcium-dependent phospholipid-binding proteins (2) that are involved in a wide range of biological processes, such as the formation of the cell membrane and cytoskeleton; the regulation of cell signal transduction and inflammation; cell proliferation; apoptosis; autophagy; and the regulation of extracellular matrix integrity (3,4). Structurally, annexins are hallmarked by a highly alpha-helical and tightly packed protein core domain, consisting of four similar repeats approximately 70 amino acids long (5), that is considered a Ca^{2+}-regulated membrane-binding module. However, studies have shown that annexins A1, A2, A5 and B12 have significantly different Ca^{2+}-dependent membrane-binding properties due to their ability to form Ca^{2+}-dependent membrane-bound trimers (2,6). This feature may be associated with their second principal domains, which are responsible for the distinct localizations and specialized functions of the proteins through posttranslational modification and binding to other proteins (6). A recent study suggested that more than one thousand annexin superfamily proteins have been identified, mainly in only eukaryotic phyla and not in yeasts or prokaryotes (5). The human annexin superfamily comprises 13 members, the majority of which are frequently dysregulated in cancer (7).

The structure and function of ANXA1

ANXA1, a 37 kDa protein, was the first member of the annexin superfamily to be discovered (6,8) and has been widely studied only in the context of inflammation resolution at the outset. An increasing number of studies have reported ANXA1 deregulation in numerous cancers, and further in-depth studies have suggested that it regulates the occurrence and metastasis of cancer at different levels (9). ANXA1 consists of 346 amino acids and has two distinct structural regions: a single N-terminal domain, also known as the tail, and a C-terminal domain, called the core domain. The C-terminus has Ca^{2+} and membrane-binding sites that regulate the release and exposure of the N-terminus, similar to a separate conformational switch. Then, the exposed N-terminus allows ANXA1 to interact with different ligands, enabling the modification (e.g., phosphorylation, glycosylation, acetylation, and lipidation) of many potential sites. This unique structure endows ANXA1 with a variety of biological functions (10). ANXA1, a Ca^{2+}-dependent phospholipid-binding protein, plays a regulatory role in not only adhesion, apoptosis, cytoskeletal protein reorganization, angiogenesis, differentiation, inflammation, and immunity but also cancer cell proliferation, invasion and metastasis (3,9,11-13).

Expression and role of ANXA1 in tumors

Numerous studies have reported that ANXA1 expression is dysregulated in various common malignant tumors, including nonmetastatic gliomas (14-17) and metastatic tumors. Among the metastatic tumors, ANXA1 is mainly upregulated in pancreatic cancer (PC) (18-21), multiple myeloma (MM) (22), nasopharyngeal carcinoma (NPC) (11,12), oral squamous cell carcinoma (OSCC) (23),

Table 1 The search strategy summary

Items	Specification
Date of search	May 2022
Databases and other sources searched	PubMed
Search terms used	See Table S1
Timeframe	November 1994 to April 2022
Inclusion and exclusion criteria	Inclusion criteria: English research papers and review
Selection process	Lulu Zheng and Lanxin Li initially screened out the literature related to the theme, and then Xiaoqiu Liang and Ailan Cheng discussed the final literature to use

Table 2 Expression and roles of ANXA1 in the various common malignant tumors

Tumor types	Species	Tissue types	Cell lines	Expression	Role	References
Metastatic tumors						
Breast cancer	Human	Adenocarcinoma	MCF-7, T-47D, SK-Br-3, ZR-75-1/all TNBC cell lines	–/+++	Promotes invasion, prognostic biomarkers	(36-39)
Gastric cancer	Human mice	Adenocarcinoma	AGS, N87, MKN45	–/+	Inhibits cell growth, promotes invasiveness	(34,35)
Lung cancer	Human	Adenocarcinoma	H1975, H1650, A549, H1299	+++	Decrease chemosensitivity to Osimertinib; promote the tumorigenesis, invasion and migration	(27-30)
Melanoma	Human	Connective tissue	SK-MEL-5	–	Induces invasion and metastasis	(32,33)
Multiple myeloma	Human	Connective tissue	NCI-H929, RPMI-8226	+++	Its knockdown enhances chemosensitivity	(22)
Nasopharyngeal carcinoma	Human	Squamous cell carcinoma	5-8F, 6-10B	+++, ++	Promotes metastasis	(11,12)
Oral squamous cell carcinoma	Human	Squamous cell carcinoma	Tca-8113 SCC-9	+	Inhibits cell proliferation, invasion; reverses TGF-β1/EGF-induced EMT	(23)
Pancreatic carcinoma	Human	Adenocarcinoma	MIA PaCa-2	+++	Maintains a malignant phenotype	(18-21)
Papillary thyroid carcinoma	Human	Papillary adenocarcinoma	BCPAP	+++	Expedites the growth and metastasis	(24-26)
Non-metastatic tumor						
Glioma	Human	Connective tissue	U87, U251, U118, A172	+++	Inhibits apoptosis; promotes invasion and migration, prognostic biomarkers	(14-17)

–: Negative; + to +++: low to high. ANXA1, annexin A1, annexin I; TNBC, triple negative breast cancer; TGF-β1 transforming growth factor-β1; EMT, epithelial-mesenchymal transition.

papillary thyroid carcinoma (PTC) (24-26), lung cancer (27-30), and colorectal cancer (31) and downregulated in melanoma (32,33) and esophageal and bile duct cancers (34); moreover, its expression in gastric cancer (GC) (34,35) and breast cancer (BC) (36-39) remains controversial among researchers (*Table 2*). Tumor development and metastasis are closely associated with the differential expression of ANXA1 in normal and tumor tissue samples (8). Increasing evidence has indicated that ANXA1 dysregulation and subcellular localization are involved in the development, invasion, and metastasis of various cancers in tumor type-specific patterns (4).

The role of ANXA1 in tumor development

ANXA1 may play a role in the angiogenesis of tumors. In BC cells, ANXA1 can reportedly directly activate nuclear factor-κB (NF-κB) expression by regulating miR-26b and miR-562, thereby promoting tumor-induced endothelial cell tube formation (40). In addition, a recent study showed that Ac2-26, an N-terminal ANXA1 mimetic peptide, promotes the activation of endothelial cells and affects the blood vessel formation of PC cells *in vitro*. Most importantly, these phenomena are interrupted by the interaction between heparan sulfate and ANXA1 (20). ANXA1 may contribute to the growth of some cancers (24,28,41). One recent report indicates that ANXA1 may be regulated by MYC to promote PTC proliferation (26). One study also reported that ANXA1 knockdown directly suppressed the proliferation of non-small cell lung cancer (NSCLC) cells (28). Another study demonstrated that ANXA1 was a direct target gene of miR-196a and that its knockdown reversed the inhibitory effect of miR-196a on the proliferation of EC109 esophageal squamous cell carcinoma (ESCC) cells (41). In addition, ANXA1 has been reported to promote the proliferation of other cancer cells, such as PC (42), BC (43), gastrointestinal cancer (44), and glioma (16,17) cells. The mechanisms include directly binding to formyl peptide receptor (FPR) to stimulate mitogen-activated proliferation (42), affecting G1 phase cell cycle arrest, targeting erythropoietin-producing hepatocellular receptor tyrosine kinase subtype A2 (EphA2) degradation (44), targeting the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway (16), and promoting alternative macrophage polarization in the tumor microenvironment (43). However, ANXA1 may also exert antiproliferative effects, as studies have shown that it is related to the sustained activation of the mitogen-activated protein kinase/extracellular signal regulated protein kinase (MAPK/ERK) signaling pathway, resulting in the destruction of the actin cytoskeleton and the inhibition of cyclin D1, thereby reducing the proliferation of A549 lung cancer cells and RAW264.7 macrophages (45). ANXA1 also inhibits the proliferation of OSCC (23), human laryngeal squamous cell carcinoma (46), cervical cancer (47), BC (48), and GC (34) cells. Its antitumor effect is associated with the activation of FPRs and inhibition of miR-196a in a negative feedback loop through NF-kB and c-Myc (46,48).

The role of ANXA1 in tumor migration and invasion

ANXA1 promotes both the invasion and migration of most tumors, such as the pancreatic ductal adenocarcinoma (PDAC) (42), ESCC (41,49), and NSCLC (27,28), and it facilitates only the invasion of BC (38,39,43) and GC (35) cells. In addition, ANXA1 inhibits the invasion of OSCC cells *in vitro* (23) and silencing ANXA1 reduces the migration, invasion, and proliferation of glioma cells (14).

The mechanisms by which ANXA1 regulates tumor invasion and migration are diverse. One recent study showed that ANXA1 was targeted and regulated by miR-196a to promote the invasion and migration of ESCC cells (41,49). The ANXA1-NF-κB-miR26a regulatory pathway also plays a role in the invasion and migration of NSCLC (27). ANXA1 can also increase the migration and invasion of PDAC cells by upregulating the expression and activity of matrix metalloproteinase-9 (MMP-9) (42). Additionally, the presence of secreted forms of the ANXA1 protein is thought to be responsible for its differential invasive behavior in various PC cells, as the secreted forms may be able to induce the migration and invasion of PC *in vitro* (19). ANXA1 can promote migration by activating EGFR signaling in bladder cancer and is a reliable clinical predictor for the prognosis of bladder cancer (50).

The role of ANXA1 in tumor metastasis

Metastasis is an unsalvageable fatal stage of malignant tumors. Although multiple studies have shown that changes in ANXA1 protein expression are closely related to the metastasis of various tumors, the results of these studies are contradictory. High ANXA1 expression is positively correlated with tumor metastasis, which is mainly manifested in PC (18,19), melanoma (32), NPC (11,12), PTC (25), and positive BC (51-53). However, the downregulation of ANXA1 has been confirmed to be associated with the distant metastasis of NSCLC (54) as well as the metastatic mouse and human BC cell lines (37,55,56). At present, the expression and functional roles of ANXA1 in BC remain controversial (53,57).

In different locations, ANXA1 affects tumor metastasis in different forms by many mechanisms in cancer cells. Extracellular ANXA1 can activate FPRs to affect metastasis by favoring cell migration and invasion, which is consistent with the finding that Ac2-26 significantly increases the cell migration/invasion rate by inducing the release of intracellular calcium (19). In addition, intracellularly, the

ANXA1 protein can regulate metastasis by preserving cytoskeletal integrity and maintaining a malignant phenotype *in vitro*, which is independent of the FPR pathway (18). Another study reported that ANXA1 may increase metastatic potential via the constitutive activation of NF-κB, caused by its interaction with IKKγ, which can recruit RIP1 to the IκB kinase complex (58).

ANXA1 can also decrease its own expression through various mechanisms, such as allelic loss (59), gene methylation (60), p53 mutation causing reduced promoter activity (61), and mRNA degradation acceleration by endogenous microRNAs (miRNAs) (62,63), which affects tumor metastasis.

Clinical application of ANXA1

ANXA1 was originally identified as a regulator of inflammation and immunity. In recent years, its clinical application in the oncology field has gradually been explored, and it has been shown to play roles in tumor prevention, diagnosis, therapy, therapeutic efficacy evaluation and prognosis evaluation. The ANXA1 molecule is pluripotent and of great interest due to its strong potential clinical implications. However, ANXA1 cannot be classified simply as a tumor suppressor or promoter, as its expression levels and effects in the same tumors remain controversial. These differential effects are the main factor limiting its clinical application.

The role of ANXA1 in tumor apoptosis

Increasing evidence suggests that apoptosis, a form of programmed cell death, plays an important role in regulating tumor growth and responses to various cancer treatments, including radiotherapy and chemotherapy, and the regulation of apoptosis may be an effective way to improve the efficacy of tumor treatments (64). In recent decades, promoting the effective elimination of cancer cells by apoptosis has been a mainstay and goal of clinical cancer therapies (65). ANXA1 is closely related to tumor apoptosis, and the elucidation of this relationship contributes to the design and development of therapeutic strategies based on rational molecular approaches that aim to modulate apoptotic pathways.

ANXA1 is involved in the apoptosis of cancer cells induced by many chemicals. ANXA1 promotes the apoptosis of not only lung epithelial cells infected with influenza type A viruses and myelomonocytic lineage cells but also tumor cells through the intrinsic apoptotic pathway (66-69). ANXA1 has differential effects on the apoptosis of cells treated with different doses of FR235222, a novel histone deacetylase inhibitor in human promyelocytic leukemia U937 cells, human chronic myelogenous leukemia K562 cells and human T-cell leukemia Jurkat cells (70). However, in prostate cancer cells, the inhibition of ANXA1 expression is related to reduced levels of apoptosis induced by FR235222 regardless of the dose (71). In addition, a recent study showed that the modulation of ANXA1 expression is correlated with the punicalagin-induced apoptosis of colorectal cancer cells (72). In various cancers, the effects of ANXA1 expression on apoptosis also differ. The overexpression of ANXA1 in human histiocytic lymphoma cells and bronchoalveolar epithelial cells is reported to promote apoptosis, which is associated with the activation of Caspase-3 and transient intracellular calcium influx (66,68,73). However, in other cancers, antagonizing ANXA1 expression promotes cell apoptosis (14,16,30,74).

The role of ANXA1 in tumor drug resistance

Chemotherapy is an important cancer treatment modality, and its effectiveness is challenging (75). Inherent or adventitious drug resistance to chemotherapy can result in poor treatment outcomes and tumor relapse, a major cause of treatment failure (76). The expression of ANXA1 plays a key role in chemotherapy resistance, and regulating ANXA1 expression represents a possible strategy for overcoming resistance. ANXA1 can potentially predict resistance to antitumor drugs, including trastuzumab, gemcitabine, 5-fluorouracil, cisplatin, docetaxel, and doxorubicin, and serves as a novel target for improving the chemosensitivity of cancers, such as oral cancer, MM, NSCLC, esophageal carcinoma, GC, PC, renal cell carcinoma and colorectal cancer.

Currently, chemotherapy plus trastuzumab remains a standard therapeutic strategy for patients with human epidermal growth factor receptor 2-BC (77). Trastuzumab is remarkably effective, and reducing its resistance can benefit more patients. Concerning trastuzumab resistance, the results of the Fin-her phase III randomized trial indicated that the ANXA1 metagene is a novel predictive biomarker of resistance to adjuvant trastuzumab (78). However, the latest research shows that ANXA1 protein expression is not predictive of trastuzumab resistance but is associated with BC mortality and recurrence (52). Gemcitabine, 5-fluorouracil, and doxorubicin are the main antitumoral agents used in clinical practice. In primary PC cell lines, ANXA1 expression is related to drug responses;

for example, high levels are positively associated with sensitivity to gemcitabine and doxorubicin and negatively associated with sensitivity to 5-fluorouracil (79). In PDAC cells, the downregulation of ANXA1 promotes resistance to gemcitabine and 5-fluorouracil through the protein kinase C/c-Jun N-terminal kinase/P-glycoprotein (PKC/JNK/P-GP) signaling pathway (80). Nevertheless, in ANXA1 knockout (KO) MIA PaCa-2 PC cells, ANXA1 was not shown to be involved in the apoptosis process mediated by gemcitabine (18). Additionally, in oral cancer cells, reduced ANXA1 expression promotes chemosensitivity to cisplatin, docetaxel, and 5-fluorouracil chemotherapy by enhancing caspase-dependent apoptosis (74). Arsenic trioxide, which functions by inducing apoptosis, was originally used as a treatment for patients with acute promyelocytic leukemia. Arsenic trioxide was later found to have an inhibitory effect on neuroblastoma, head and neck, esophageal, gastric, and cervical cancer cells by disrupting the cell cycle and has thus become an antitumor agent. One study reported that the specific silencing of ANXA1 enhanced the sensitivity of cancer cells to a low concentration of arsenic trioxide by inhibiting MAPK/ERK activation (81). The knockdown of ANXA1 enhances chemosensitivity to bortezomib, one of the most frequently used drugs in the treatment of MM (22). In NSCLC, regardless of whether epidermal growth factor receptor mutations are present, ANXA1 is correlated with chemotherapeutic resistance to osimertinib and cisplatin (29,30). Stabilization of ANXA1 by RRM2 can activate the AKT pathway, thereby promoting resistance to sunitinib in renal cell carcinoma (82).

The role of ANXA1 in tumor-targeted therapy

In tumors, ANXA1 is a valuable novel target for research on therapeutic drugs targeting tumor growth, migration, and invasion (10). Its peptide mimetics have been widely researched for use in a variety of diseases, such as neuroinflammatory diseases (83), eye diseases (84,85), cardiovascular disease (86,87), and gastroenteritis (88), and have shown great potential in therapies targeted at certain tumors, such as NPC (11), gastric and colon cancer (44), and melanoma (32). NPC patients receiving chemoradiotherapy have an extremely poor quality of life and severe side effects such as bone suppression. A11, an ANXA1-derived peptide, occupies the binding sites of ANXA1 and EphA2, thereby blocking the binding of the two proteins, and significantly inhibiting the proliferation, invasion, and metastasis of NPC (11). This targeted therapy blocks signal transmission by targeting specific molecules related to tumor progression in and around NPC cells, thereby inhibiting the occurrence and development of NPC, can accurately identify and treat NPC cells with low toxicity and side effects and has broad prospects in the clinical treatment of NPC (89).

The role of ANXA1 in tumor prevention, diagnosis, and prognostic evaluation

Numerous studies have shown that ANXA1 not only regulates inflammation and immunity (90-92) but also has potential as a novel marker for the screening (93,94), diagnosis (95,96), treatment efficacy prediction (97) and prognostic prediction (15,98,99) of tumors. ANXA1 can enhance the function of Treg cells and reduce the survival rate of patients with BC (100). In addition, ANXA1 plays a role in cancer prevention, as monoubiquitinated nuclear ANXA1 was shown to inhibit chemical-induced mutagenesis potentially by preventing DNA damage-induced gene mutations, ultimately conferring cancer chemoprevention (101).

EMT

Classification of EMT

EMT, a reversible conversion process characterized by the loss of epithelial cell features and the gain of mesenchymal phenotypes, can confer stem cell characteristics, reduce apoptosis and senescence, and promote immunosuppression (102,103). EMT occurs in three distinct conditions and is thus divided into three types based on its mechanisms of induction and progression, which vary dramatically among conditions. The first type is related to implantation, embryogenesis, and organ development, which are driven by the evolutionary need to remodel and diversify tissue to enable proper morphogenesis and generate a functional organism. The second type is associated with tissue regeneration and fibrosis, which depends on inflammation-inducing injuries for its initiation and continued occurrence. In the case of injury, the tissue is repaired by generating activated mesenchymal cells, notably myofibroblasts that produce excessive amounts of the collagen-rich extracellular matrix. Type 3 EMT occurs in the context of tumor growth and cancer progression, which is facilitated by the genomic alterations acquired by cancer cells and this type generates cells with invasive properties that enable them to move into the bloodstream and spread systemically to other organs (104-107). Therefore, EMT not only participates in embryonic development, wound healing and fibrosis but also plays a key role in cancer metastasis (102,103). For

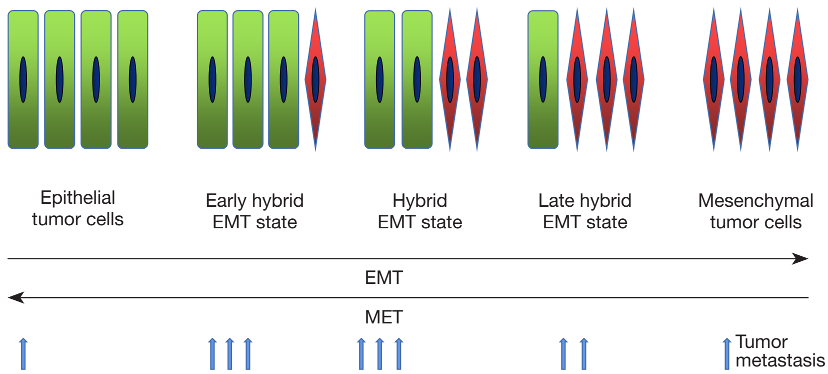

Figure 1 Different EMT transition states. The different EMT transition states represent multiple tumor subpopulations ranging from epithelial to completely mesenchymal states, passing through intermediate hybrid states. The hybrid EMT state is the most correlated with increased metastatic potential. EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition.

transition and transition-primed tumor epithelial cells, the occurrence of type 3 EMT is an important mechanism for movement, invasion and metastasis.

Common biological characteristics of EMT

Normally, sharp changes in the expression of selected epithelial and mesenchymal markers are regarded as evidence of EMT. Among them, the most common markers of epithelial traits are E-cadherin, occludins, and cytokeratins, while N-cadherin and vimentin are more common mesenchymal markers. These cell molecular markers are associated with the epithelial and mesenchymal state, affecting the disassembly of epithelial cell–cell junctions and the dissolution of apical-basal cell polarity (102,105). Pathologists usually regard the detection of these EMT-related protein markers as highly specific indicators of high-grade malignant tumors (106). Interestingly, the clinical prognosis depends on the co-expression of epithelial and mesenchymal markers, rather than on the fully epithelial or mesenchymal phenotype (108).

EMT-inducing transcription factors (EMT-TFs)

Upon the expression of EMT-TFs induced by signals derived from the tumor-associated reactive stroma that act on carcinoma cells, EMT is activated in carcinoma cells. EMT-TFs can orchestrate the expression of various components of the EMT program, such as ZEB, SNAIL and TWIST, which inhibit the expression of molecular markers associated with the epithelial state and concomitantly activate the expression of molecular markers associated with the mesenchymal state. Many variations of the EMT program play roles in normal tissues and neoplastic growth depending on the diverse expression of EMT-TFs (104). The considerable variability and tissue specificity of the roles and functions of different EMT-TFs (109), which determine the complexity of the mechanism of EMT, need to be further studied.

The relationship between EMT and tumor metastasis

EMT, as a complex biological transformation process, is considered to be important for cancer invasion and metastasis (110-115). During EMT, epithelial cells lose their apical-basal polarity and acquire a more mesenchymal and motile phenotype followed by cell-to-cell contact disintegration (113). These mesenchymal phenotype cells have a stronger ability to infiltrate and metastasize than epithelial cells (104). Neoplastic cells are in an epithelial-like state in early-stage carcinomas, and more mesenchymal characteristics are gradually acquired as tumor progression proceeds (104). Increasing the mobility and invasiveness of cancer cells by acquiring EMT characteristics is an important mechanism of metastasis (18,112).

The latest research shows that EMT occurs through distinct intermediate states rather than via a binary process, and multiple tumor subpopulations are associated with different degrees of EMT in various cancers. The plasticity, invasiveness and metastatic potential of these subpopulations differ (116). In different stages of EMT (from epithelial to completely mesenchymal states, passing through intermediate hybrid states), the hybrid EMT state is the most correlated with increased metastatic potential (108) (*Figure 1*).

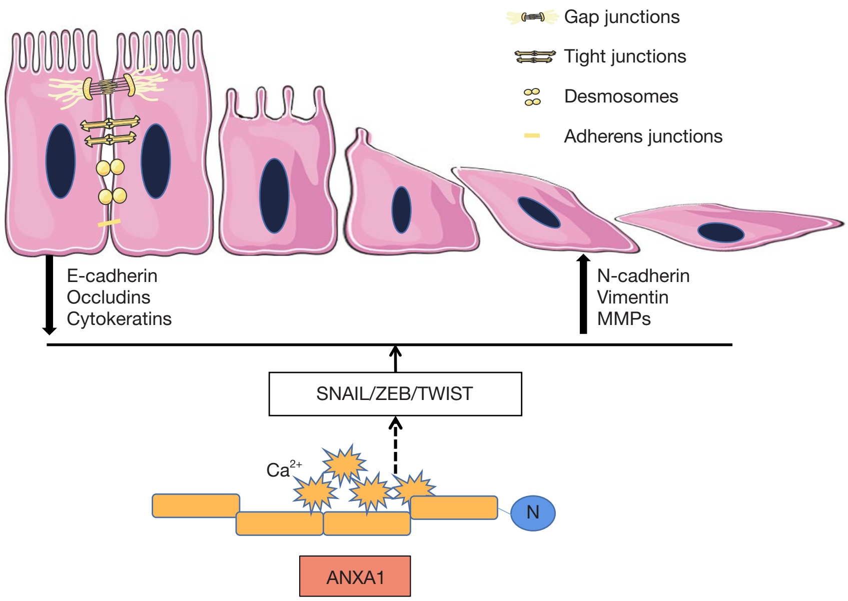

Figure 2 Relevant pathological biomarkers of EMT. MMP, matrix metalloproteinase; ANXA1, annexin A1, annexin I; EMT, epithelial-mesenchymal transition.

ANXA1 acts on EMT through different mechanisms to affect tumor metastasis

During the process of tumor progression, EMT enables tumor cells to acquire a more aggressive and metastatic mesenchymal phenotype, thereby promoting tumor metastasis. However, ANXA1 can promote the occurrence of EMT in different forms through different pathways to affect tumor metastasis (*Figure 2*). In most cases, ANXA1 does not act on EMT directly but rather affects the expression of EMT-TFs after interacting with certain factors (such as FPRs and miRNAs) or activating cell signaling pathways through certain physiological processes (such as autophagy), thereby affecting the occurrence of EMT (*Figure 3*). We can regard these factor inhibitors or signaling pathway inhibitors as potential therapeutic targets affecting tumor metastasis since they can block the effect of ANXA1 on EMT, thereby further prolonging the lives of cancer patients (*Table 3*).

ANXA1 promotes EMT through different signaling pathways

Several activated intracellular signaling events can induce EMT when epithelial cells encounter specific signals during normal development, wound healing and carcinoma progression (104,125). These pathways include the transforming growth factor-β (TGF-β), wnt signaling, Notch, PI3K/AKT, MAPK/ERK, p38 MAPK and c-Jun N-terminal kinase (JNK) pathways.

Multiple studies have shown that EMT activated by ANXA1 through the TGF-β signaling pathway plays a key role in the invasion and migration of BC. ANXA1 is similar to an EMT switch, which promotes the formation of basal BC cell metastasis by enhancing TGF-β/Smad signaling and actin reorganization (36,126). ANXA1 can also specifically bind directly and closely to the DC-STAMP domain containing 1-antisense 1 to alter its own expression, which promotes TGF-β-induced EMT processes (117). Paradoxically, another study revealed that ANXA1 could efficiently suppress TGF-β-independent EMT to inhibit the metastasis of BC (37). In addition, in BC cells, ANXA1 induces the constitutive activation of NF-κB by interacting with the IκB kinase complex. This phenomenon further significantly enhances the gene expression of MMP-9, which is closely related to EMT (118), to induce tumor invasion and migration (58,119). Due to the heterogeneity of BC, the effects of the relationship between ANXA1 and EMT on BC cell behavior remain controversial (57).

ANXA1 can also activate the PI3K/AKT pathway, a classic pathway of oncogenic transformation (127), to promote the growth of colorectal cancer and the invasion and metastasis of NPC (12,31). Specifically, as a membrane protein,

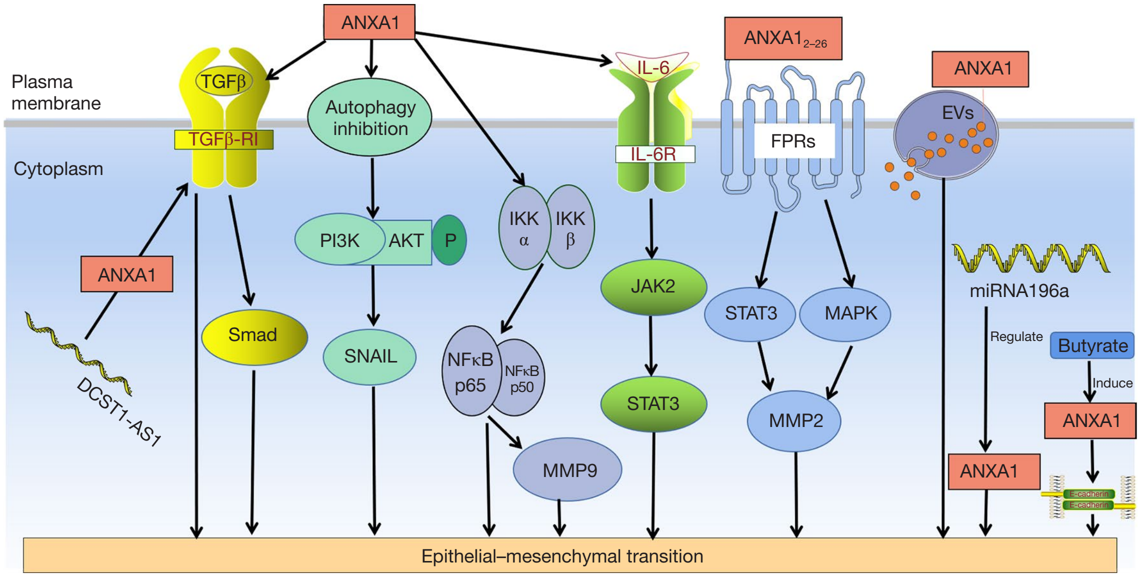

Figure 3 ANXA1 regulates the occurrence of EMT via different mechanisms to thereby affect tumor metastasis. ANXA1 regulates the expression of EMT-TFs or activates cell signaling pathways after interacting with a substance to regulate EMT via different mechanisms, thereby influencing tumor metastasis. ANXA1, annexin A1, annexin I; TGF-β, transforming growth factor-β; PI3K, phosphoinositide 3-kinase; IKK, the IkappaB kinase; NF-κB, nuclear factor-κB; MMP, matrix metalloproteinase; IL, interleukin; JAK2, Janus kinase 2; STAT3, signal transducers and activators of transcription 3; FPRs, formyl peptide receptors; MAPK, mitogen-activated protein kinase; EVs, extracellular vesicles; MiRNA, microRNA; TF, transcription factor.

Table 3 ANXA1 promotes EMT through different mechanisms

Mechanisms	Inhibitor	Ref
Signaling pathways		
The TGF-β signaling pathway		(36,37,117)
The PI3K/AKT/mTOR signaling pathway		(12)
The NF-κB signaling pathway		(118,119)
The IL-6/JAK2/STAT3 signaling pathway		(25)
Interacts with FPRs	CHIPS, CsA, ICT12035, CsH	(32,51,120-122)
A component of tumor-derived EVs		(123)
Accepts transcriptional regulation by miRNA196a		(124)
Induced by butyrate		(33)

ANXA1, annexin A1, annexin I; EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor-β; PI3K, phosphoinositide 3-kinase; mTOR, the mechanistic target of rapamycin; NF-κB, nuclear factor-κB; IL-6, interleukin 6; JAK2, Janus kinase 2; STAT3, signal transducers and activators of transcription 3; FPRs, formyl peptide receptors; CHIPS, chemotaxis inhibitory protein of S. aureus; CsA, cyclosporin A; CsH, cyclosporin H; EVs, extracellular vesicles.

ANXA1 is a component of the lysosomal membranes and is involved in the development of autophagosomes. It can activate the PI3K/AKT signaling pathway, leading to Beclin-1- and ATG5-dependent autophagy inhibition, and further inducing EMT-like alterations, thereby affecting the migration, invasion and metastasis of NPC (12).

In addition, the mechanisms underlying the Janus kinase 2/signal transducers and activators of transcription

3 (JAK2/STAT3) pathway have been extensively studied, and most are known to play roles in the invasion and metastasis of tumors by affecting EMT processes, including the mechanism by which ANXA1 affects PTC (128,129). ANXA1 can regulate malignant PTC phenotypes by regulating the interleukin 6 (IL-6)/JAK2/STAT3 signaling network and thereby influencing the dynamic properties of EMT (25).

ANXA1 interacts with FPRs to promote EMT

FPRs, which are a seven-transmembrane, G protein-coupled receptors, consist of the three proteins: PPR1, FPR2 (formerly known as ALX or formyl peptide receptor like-1) and FPR3 (formerly known as formyl peptide receptor like-2) (120). By interacting with ANXA1, FPRs play an important role in tumor proliferation, invasion and metastasis (51,120,130,131) and activate components of the tumor microenvironment (132). Recently, ANXA1 was reported to polarize macrophages to an alternatively activated subtype (M2). These cells then bind to FPR2, triggering the G protein-coupled receptor-mediated signaling cascade to thereby modulate cytokine signaling and the tumor microenvironment and promote the growth and migration of BC cells (43). In addition, FPRs can be activated by the annexin 1 peptide, derived from the unique N-terminal domain of ANXA1 (133). The interaction between ANXA1 and FPRs can lead to the occurrence of EMT via different mechanisms. In melanoma, the activation of matrix metalloproteinase-2 (MMP-2), followed by EMT, occurs through the MAPK and STAT3 pathways after Ac2-26 interacts with FPRs (134). It is worth noting that MMP-2 can efficiently degrade collagen IV and laminin and thus help melanoma cells to cross the basement membrane, which is crucial for EMT (135). Another study showed that ANXA1 can regulate EMT in cE1 cells, a prostate cancer cell line from a mouse model, and that the ANXA1/FPR interaction confers a stem cell-like phenotype to cancer cells (136). Inhibiting the activation of FPR1 by FPR1 inhibitors, such as a chemotaxis inhibitory protein of S. aureus (121), cyclosporin A (51), ICT12035 (120), and cyclosporin H (122), which blocks the effect of ANXA1 on EMT, is a potential strategy for reducing cell motility and tumor cell activation and inhibiting cell growth and invasion. These phenomena were confirmed by a study on the use of cyclosporin A to disrupt the activation of the ANXA1/FPR1 autocrine axis and thereby reduce MDA-MB-231 BC cell growth and aggressiveness *in vitro* and *in vivo* and might be a therapeutic target for triple-negative BC (51). Notably, some researchers have proposed that FPR2 agonists can inhibit the continuous inflammatory process to favor reparative and regenerative processes within the patients themselves (137). Given the subtle relationship between inflammation and tumors, more studies are required to clarify the effects of FPR2 agonists on tumors.

ANXA1, a component of tumor-derived extracellular vesicles (EVs), modulates the EMT-like phenotypic switch

EVs are a group of heterogeneous cell-derived membrane structures that contain various types of biomolecules, including proteins, RNA, DNA, lipids and metabolites, and participate in a variety of physiological and pathological processes (138,139). According to their forms in biological fluids, they are mainly divided into exosomes (40–200 nm), microvesicles (0.2–2 μm), apoptotic bodies (0.5–2 μm), high-density lipoprotein particles (7–13 nm), and low-density lipoprotein particles (21–27 nm) (140). Among them, exosomes have been a research hotspot in recent years and play important roles in physiological and pathological processes such as intercellular communication, immune surveillance, inflammation, and tumor development. In PC, the ANXA1 protein could be regarded as an oncogenic factor due to its overexpression and special identity as a component of tumor-derived EVs, which can nourish the tumor microenvironment (132). The detection of EVs isolated from wild-type and ANXA1 KO PC cells in an *in vitro* MIA PaCa-2 model verified that the autocrine effect of ANXA1-containing EVs on PC MIA PaCa-2 cells can induce the progression of PC. In addition, ANXA1 plays a key role in the effects of EVs (123). One recent study also shows that ANXA1 contained in EVs can regulate macrophage polarization in tumor microenvironment and promotes PC progression and metastasis (21). Notably, extracellular ANXA1 plays an important role in the acquisition of a more aggressive PC phenotype, similar to a modulator of the EMT-like phenotypic switch (132,141). ANXA1 KO cells recover their metastatic potential only when treated with wild-type EVs, as they undergo EMT and become significantly more mobile. Therefore, the ANXA1 protein in EVs can trigger EMT in ANXA1 KO MIA PaCa-2 cells, leading to a more aggressive phenotype (123). The acquisition of a mesenchymal phenotype is essential for the metastasis of PC (18), and ANXA1 may promote this aggressive phenotype, suggesting that the protein can serve as a PC diagnostic/prognostic marker. In addition, the suppression of EMT induces PC chemoresistance to antiproliferative drugs, such as gemcitabine, suggesting that targeting EMT will enhance chemotherapeutic efficacy (110). Additionally, one recent study has shown that thyroid cancer SW579 cell-derived exosomal ANXA1 can promote tumor development and the thyroid follicular epithelial Nthy-ori3-1 cells' malignant transformation (142).

ANXA1 is transcriptionally regulated by miR-196a to promote EMT

MiRNAs are an abundant family of endogenous small noncoding RNAs (approximately 22 nucleotides) that play roles in biological processes such as cellular differentiation, proliferation, apoptosis, and synaptic plasticity by regulating target gene expression (143,144). MiRNAs significantly affect EMT and mesenchymal-epithelial transition processes by regulating key genes, such as zeb1, zeb2, snail, and twist, which are related to stem cell pluripotency and tumor progression (145). In the context of cancer, these miRNAs function as tumor suppressors or promoters. Some miRNAs, including miR-1271 (146), the miRNA-200 family (miR-200a, miR-200b, miR-200c, miR-141 and miR-429) and miR-205 (147), exert tumor suppressor functions by regulating EMT. For example, miR-1271 suppresses EMT by targeting zeb1 and twist1, thereby affecting the proliferation, invasion and migration of PC (146). MiR-200a suppresses EMT by targeting zeb1 and zeb2, delaying the growth of GC (148). However, other miRNAs play a tumor-promoting role, including miR-196 (124), by affecting EMT. In one study, the aggressive phenotype of ANXA1 KO PC cells was restored by miR-196, a well-known oncogenic factor. MiR-196 not only triggers EMT but also mediates dynamics and other protein functions, promoting the migration and invasion of PC cells (124). Both ANXA1 and miR-196a participate in the induction of mesenchymal and more aggressive phenotypes jointly or individually (18,124,149). In addition, another study reported that in ESCC, miR-196a may have directly targeted ANXA1, which potentially further regulated the expression levels of COX2, *MMP-2*, snail and E-cadherin, thereby affecting the proliferation, invasion and migration of ESCC cells (41,49). MiR-196a can also suppress ANXA1 to thereby exert an oncogenic effect on head and neck cancer cells (62). The miR-196a/ANXA1 axis may represent a therapeutic target for ESCC, head and neck cancer, BC and endometrial cancer (41,62,150). In conclusion, various miRNAs are practical therapeutic targets, and they could be targeted to inhibit tumor invasion and metastasis, potentially representing a new therapeutic strategy.

ANXA1 promotes EMT after induction by butyrate

In melanoma, multiple signaling pathways promote EMT activation, including RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and Wnt/β-catenin (125). One recent study proposed that the upregulation of ANXA1 expression induced by butyrate in a time- and dose-dependent manner regulates the expression of E-cadherin in human melanoma cells, thereby promoting their invasion via activation of the EMT signaling pathway (33). The loss of the cell–cell adhesion molecule E-cadherin can indeed lead to the uncontrolled growth and invasion of transformed melanocytes in the progression of melanoma (151). Inducing the expression of ANXA1 by butyrate, thereby blocking the occurrence of EMT, can restrict the invasion and metastasis of melanoma. This finding is consistent with the potential strategy of using synthetic and phytochemical agents to regulate the EMT signaling pathway and thereby reduce the aggressive progression of metastatic melanoma (125).

Conclusions

ANXA1 is differentially expressed in various tumors and performs numerous functions as either a suppressor or promoter of neoplastic development according to the cancer type. EMT is a highly dynamic process controlling the transdifferentiation of epithelial cells into motile mesenchymal cells (with stem cell-like properties and increased mobility and invasive ability). ANXA1 promotes the occurrence of EMT through different mechanisms. Among them, ANXA1 is known to effect EMT via distinct signaling pathways, but it remains unclear whether signaling crosstalk exists. While ANXA1 and FPR are known to interact in various tumors, which is a classical mechanism, the role of FPR inhibitors in tumors has not been fully elucidated. In addition, ANXA1 can be an EV component, be transcriptionally regulated by miR-196, and be induced by chemical drugs to promote the occurrence of EMT. ANXA1 promotes EMT by "external forces", such as miR-196a and butyrate, suggesting its important role in tumor metastasis. However, these "external forces" that can affect the ANXA1 expression in tumor cells still need to be further studied and supplemented.

Since ANXA1 is potentially a new target in the study of therapeutic drugs that combat tumor growth, migration and invasion, elucidating the mechanisms by which it affects EMT will further identify more promising cancer therapeutic targets. Overall, cancer is a serious disease that imposes a heavy burden on the health of patients, and tumor metastasis remains the most challenging aspect of cancer treatment. Future studies should elucidate the effects of ANXA1 on tumor invasion, migration and metastasis through EMT *in vitro*, *in vivo*, and ultimately in patients to identify more therapeutic targets.

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Footnote

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