

Advancements of Annexin A1 in inflammation and tumorigenesis

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Abstract: Annexin A1 is a Ca²⁺-dependent phospholipid binding protein involved in a variety of pathophysiological processes. Accumulated evidence has indicated that Annexin A1 has important functions in cell proliferation, apoptosis, differentiation, metastasis, and inflammatory response. Moreover, the abnormal expression of Annexin A1 is closely related to the occurrence and development of tumors. In this review article, we focus on the structure and function of Annexin A1 protein, especially the recent evidence of Annexin A1 in the pathophysiological role of inflammatory and cancer. This summary will be very important for further investigation of the pathophysiological role of Annexin A1 and for the development of novel therapeutics of inflammatory and cancer based on targeting Annexin A1 protein.

Keywords: Annexin A1, structure, inflammation, cancer

Introduction

Annexins constitute a class of structurally homologous calcium-dependent phospholipid-binding protein superfamily. Human-derived Annexins contain Annexin A1 to A13¹ expressed in a variety of tissues,^{2,3} which are closely related to the cell membrane and cytoskeletal components.⁴ The structure of all Annexins is similar and includes four sets of repeating amino acid sequences with about 70 amino acid residues in the core region, except for Annexin VI whose core region consists of eight sets of repeating amino acid sequences. However, the N-terminal region of the Annexins has significant differences in amino acid sequence length and residue composition,^{5,6} which determines the various biological functions of Annexins, including promoting membrane fusion⁷ and membrane transport,⁸ ion channel formation,^{9–11} regulating cell adhesion,¹² cell growth and differentiation,¹³ cell proliferation and apoptosis,^{14,15} cell migration,¹⁶ tumorigenesis,¹⁷ etc.

In the late 1970s, Annexin A1 was first identified as a member of the Annexin family.¹⁸ Initially, Annexin A1, also named as macrocortin,¹⁹ renocortin,²⁰ lipomodulin,²¹ and lipocortin I,²² was identified as the inhibitor of phospholipase A2 (PLA2).¹⁸ Thus, it was mainly used as an inhibitor of pro-inflammatory factors prostaglandins (PGs) to study the inhibition of leukocyte aggregation in an inflammatory model^{23–26} for a long time. Annexin A1 is particularly abundant in neutrophils,²⁷ but not abundant in lymphocytes.^{28–30} Annexin A1 is mainly distributed in the cytoplasm and accounts for about 2–4% of the cytoplasmic protein.³¹ A small amount of Annexin A1 is also found in the nucleus,³² but the Annexin A1 protein is mobilized to the cell surface when the cell is activated.²⁷ Furthermore,

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Annexin A1 can also stably or reversibly bind to cytoskeletal proteins, regulating the interaction of cells with extracellular matrix.³¹ In this review, we mainly focus on the pathological role of Annexin A1 in inflammation and tumorigenesis.

Structure of Annexin A1

The Annexin A1 gene is located on human chromosome 9q21.13,³³ which consists of a C-terminal core region and a uniquely functional N-terminal region with a molecular weight of 37 kDa.³⁴

The C-terminal core region of Annexin A1 is composed of four homologous repeats of about 70 amino acids, and each domain consists of five α -helices that tightly compress the repeats to form a slightly curved disc-like structure.³⁵ The four sets of repeats are arranged in a periodic manner; that is, repeats I, IV, II, and III sequentially form a structurally stable and hydrolysis-resistant compact structure by hydrophobic interaction.^{36–39} This core region contains multiple calcium-binding sites that bind to phospholipids in a calcium-dependent manner.³⁶

The N-terminal domain of Annexin A1 is composed of 44 amino acids, in which the first 26 amino acids form two α -helices of Ala²-Asn¹⁶ and Glu¹⁸-Lys²⁶ with 60° reverse tilt on Glu.¹⁷ The non-structural peptide Ser²⁷-Asn⁴³ plays a crucial role in linking the N-terminal region to the core region.³⁶ Hall et al⁴⁰ found that Thr,²⁴ Ser,²⁷ Ser,²⁸ and Thr⁴¹ have phosphorylation sites of protein kinase C (PKC) by MS/MS. Tyr²¹ is the phosphorylation site of epidermal growth factor receptor kinase, Ser⁵ is the phosphorylation site of TRMP7, and there are glycosylation, acetylation, acrylation, and proteolytic sites on other amino residues.^{41,42} This post-translational modification of Annexin A1 allows Annexin A1 to be involved in the regulation of various pathophysiological processes both inside and outside the cell. The N-terminus of Annexin A1 has a similar region to the SH2 recognition domain,

which may form a protein complex with a protein containing the SH2 domain and participate in intracellular signaling.⁴³ S100A11 (also named S100C)⁴⁴ is a calcium-binding protein with a molecular weight of 10 kDa, which has the ability to change the properties of Annexin A1 through binding to the N-terminal 10–14 amino acid residue of Annexin A1.¹ Annexin A1 has been described as a protein with membrane aggregating properties, in which the core region of Annexin A1 binds to the cell membrane mediated by calcium ion, while the exposed N-terminus has three modes of action: 1) interaction of the exposed N-terminus with a second bilayer; 2) dimerization of two such Annexin A1 via their exposed N-terminus; 3) linking of the concave faces of two such Annexin A1 molecules via an S100A11 dimer.^{36,45} The pattern structure diagram of Annexin A1 was shown in Figure 1.

Functions of Annexin A1

The role of Annexin A1 in inflammation

Inflammation is a defense response that occurs when the body's tissues are damaged, and plays an important role in restoring tissue homeostasis,^{46,47} as well as inflammation has been recognized as a hallmark of cancer.⁴⁸ In general, inflammation is beneficial to the body; however, when inflammation is uncontrollable or cannot be eliminated, it can also cause further damage to the body involved in many kinds of chronic diseases including asthma,⁴⁹ lung injury,⁵⁰ ischemia-reperfusion injury,⁵¹ atherosclerosis,⁵² multiple sclerosis,⁵³ rheumatoid arthritis,⁵⁴ rhinitis,⁵⁵ immune dysregulation,⁵⁶ and cancer.^{48,57}

Annexin A1 exhibits anti-inflammatory and pro-inflammatory effects in a variety of inflammatory experimental models^{28,58} (summarized in Table 1), and its anti-inflammatory effects are mainly regulated by formyl peptide receptor family (FPRs) signaling pathways. FPRs are G-protein coupled receptors (GPCRs) with seven trans-membrane structures, which are composed of FPR1 (FPR,

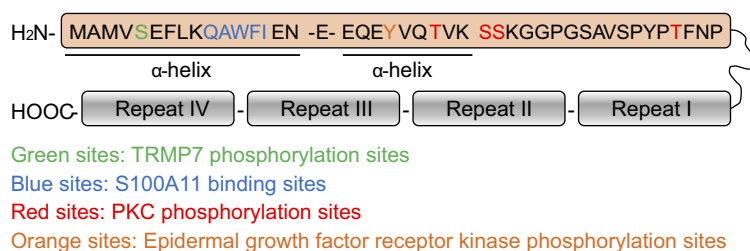


Figure 1 Pattern structure diagram of Annexin A1. The C-terminal core region of Annexin A1 is composed of four homologous repeats, while the N-terminal domain is composed of 44 amino acids with two α -helix. The N-terminal domain contains S100A11 binding sites and could be phosphorylated by TRMP7, PKC, and epidermal growth factor receptor kinase.

Table I Anti-inflammatory and pro-inflammatory roles of Annexin A1

Source of Annexin A1	Disease model	Effects observed	Suggested role of Annexin A1	Reference
Endogenous				
Annexin A1 ^{-/-} mice	Arthritis	Deficiency of Annexin A1 also abrogated glucocorticoid-dependent inhibition of cytokine and chemokine gene expression in the inflamed synovium	Anti-inflammatory	¹²⁶
Annexin A1 ^{-/-} mice	EAE	Decreased signs of the disease and reduced infiltration of T cells in the spinal cord	Pro-inflammatory	¹²⁷
Annexin A1 ^{-/-} mice	Endotoxaemia	LPS generated a deregulated cellular and cytokine response with a marked degree of leukocyte adhesion in the microcirculation	Anti-inflammatory	⁷⁴
Annexin A1 ^{-/-} mice	DSS-induced colitis	Annexin A1 is a role in the protective and reparative properties of the intestinal mucosal epithelium	Anti-inflammatory	²⁵
Annexin A1 ^{-/-} mice	NASH	Increased macrophage recruitment and exacerbation	Anti-inflammatory	¹²⁸
Exogenous				
WKYMVm-NH2	IAV	Agonist WKYMVm-NH2 decreased survival and increased viral replication and inflammation after IAV infection	Pro-inflammatory	⁸⁸
Ac2-26	Cardiovascular disease	Blockade of leukocyte recruitment, decreasing vascular permeability	Anti-inflammatory	⁶⁸
Annexin A1	Pleurisy	Inducing neutrophil apoptosis and increasing efferocytosis by macrophages	Anti-inflammatory	¹²⁹
Ac2-26	Intestinal mucosal inflammation	Accelerated healing of murine colonic wounds after biopsy-induced injury and recovery following experimentally induced colitis	Anti-inflammatory	¹³⁰
Annexin A1	SJS and TEN	Annexin A1-FPR1 interaction contributes to necroptosis of keratinocytes	Pro-inflammatory	¹³¹
Annexin A1	RA	Treatment of RA patients with steroid decreased Annexin A1 expression in T cells, GCs suppress Annexin A1 expression in T cells	Anti-inflammatory	¹³²
Ac2-26 or Annexin A1	Atherosclerotic lesions	Increased myeloid cells recruitment via Annexin A1/FPR2 signaling	Anti-inflammatory	¹³³
Ac2-26 or Annexin A1	MI	Against myocardial I-R injury, limiting neutrophil infiltration, preserving cardiomyocyte viability and contractile function	Anti-inflammatory	⁶⁹

Notes: Ac2-26: N-terminal fragment of Annexin A1 (residues 2–26); WKYMVm-NH2: N-terminal fragment of Annexin A1 (residues 1–6).

Abbreviations: EAE, experimental autoimmune encephalomyelitis; DSS-induced colitis, dextran sulfate sodium(DSS)-induced colitis; NASH, nonalcoholic steatohepatitis; IAV, influenza A virus; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; RA, rheumatoid arthritis; MI, Myocardial infarction.

NFPR, FMLP, FMLPR), FPR2/ALX (FPRL1, FPRH1, RFP, LXA4R, ALXR, HM63, FMLPX, FPR2A), and FPR3 (FPRL2, FPRH2, FMLPY).⁵⁹ A large number of agonists (ANXA1, Ac2-26, mitochondrial formyl peptide, LL-37, lipoxin A4, MMWLL, AG-14, etc.) and antagonists (CHIPS, FLIPr, CsA, CDCA, etc.)^{59–61} can bind to FPRs. Annexin A1 and its N-terminal active peptide fragment Ac2-26²⁹ bind to FPRs and initiate a downstream cascade of FPRs, promoting phosphorylation of extracellular regulated kinase (ERK) and mitogen-activated protein kinase (MAPK), thereby stimulating physiological effects.^{62–67} Annexin A1 and Ac2-26 exert anti-inflammatory effects on myocardial and cerebral ischemia-reperfusion injury by

FPR2/ALX.^{68,69} Glucocorticoids are the first class of endogenous anti-inflammatory mediators that have been successfully used in therapy.^{70,71} It has been found that the synthesis and function of Annexin A1 are regulated by glucocorticoids,^{72,73} which inhibits the expression of pro-inflammatory cytokine IL-6 and TNF.^{74,75} Annexin A1 was released in neutrophils and macrophages by autocrine or paracrine means after glucocorticoid induction.²⁸ Annexin A1 binds to FPR2/ALX and regulates ERK/MAPK signaling pathway which affects the activities of the downstream transcription factors AP1, NF-κB, and NFAT, thereby regulating the activity, proliferation, and differentiation of T cells and exerting corresponding anti-inflammatory effects, in contrast

to the regulative effects of glucocorticoids on T cell receptors (TCR).²⁸ Annexin A1 inhibits phospholipase A2 activity,¹⁴ prevents the formation of inflammatory precursors of arachidonic acid,⁷⁶ induces the formation of anti-inflammatory factors, and inhibits the formation of COX-2 and nitric oxide synthase,^{77,78} inhibits neutrophil activity and migration, inhibits the synthesis and release of inflammatory factors. Moreover, the externalization of Annexin A1 provides a failure safety mechanism to promote the clearance of apoptotic cells and inhibit the secretion of pro-inflammatory factors by macrophages.⁷⁹ The anti-inflammatory role of high-density lipoprotein was mediated through up-regulating Annexin A1 in vascular endothelial cells.⁸⁰ Collagen IV (Col IV)-targeted nanoparticles (NPs) containing Ac2-26 prevent or attenuate inflammatory responses against advanced atherosclerosis in hypercholesterolemic mice.⁸¹ Annexin A1, which interacts with the FPR family, may have a significant role in mitigating ischemia-reperfusion injury associated complications.⁸² Annexin A1, Ac2-26, lipoxin A4, and ATL (15-epi-lipoxin A4) played a positive role in the return from inflammation.^{83–85} These anti-inflammatory mediators act at different stages of the inflammatory response and are involved in impeding leukocyte aggregation, inhibiting cytokine release, promoting apoptosis, stimulating autophagy, and vascular permeability deterioration^{84,85} through FPRs.^{60,86}

Conversely, Annexin A1 also has a pro-inflammatory effect in certain inflammations. Annexin A1 can be phosphorylated by PKC and is subsequently translocated to the nucleus of BV-2 microglial cells after oxygen-glucose deprivation/reoxygenation, resulting in the induction of pro-inflammatory cytokines.⁸⁷ Annexin A1 fragment (33 kDa), formed by proteolytic hydrolysis of calpain 1 at the N-terminus of Annexin A1 (37 kDa), can activate ERK1/2 signaling activity in endothelial cells and increase the accumulation of intracellular adhesion molecule 1 (ICAM1) around neutrophils, which allows neutrophils to be immobilized on endothelial cells to enhance the trans-endothelial migration capacity of neutrophils.¹⁶ The N-terminal peptide WKYMVm-NH2 of Annexin A1 promotes viral replication and enhances the inflammatory response by activating FPR2/ALX in influenza A virus.⁸⁸ The mechanisms of Annexin A1 involved in inflammation response are summarized in Figure 2.

The role of Annexin A1 in tumorigenesis

Recent studies have shown that the expression of Annexin A1 in tumors is tissue specific. Annexin A1 is highly

expressed in colorectal cancer,⁸⁹ lung adenocarcinoma,⁹⁰ pancreatic cancer,⁹¹ liver cancer,⁹² and glioma,⁹³ down-regulation or deletion in cervical cancer,⁹⁴ thyroid cancer,⁹⁵ laryngeal cancer,⁹⁶ prostate cancer,⁹⁷ head and neck cancer.⁹⁸ In addition, the expression of Annexin A1 in gastric cancer,^{77,99–101} breast cancer,^{102,103} esophageal cancer,^{104–106} cholangiocarcinoma^{77,107–109} is still controversial. The mechanism of Annexin A1 involved in tumorigenesis is summarized in Figure 3.

Annexin A1 and gastrointestinal cancer

The expression of Annexin A1 was analyzed from 1,072 Chinese gastric cancer patients using immunohistochemistry, which showed that complete loss of Annexin A1 expression was observed in 691 (64%) of the 1,072 primary tumors and 146 (86%) of 169 nodal metastases correlated significantly with poor survival rates.⁹⁹ Annexin A1 was widely expressed in adult gastrointestinal tissue.⁷⁷ Exogenous overexpression of Annexin A1 significantly inhibited growth rate, colony formation, and migration ability, while interference with Annexin A1 by shRNA increased the viability of N87 cells, indicating the growth inhibition effect of Annexin A1 in gastrointestinal cancer. The negative correlation between Annexin A1 and COX-2 (cyclooxygenase-2) indicated that Annexin A1 can regulate COX-2 production to inhibit cell proliferation of gastrointestinal cancer.⁷⁷ However, Cheng et al showed that the high expression of Annexin A1 is significantly associated with stage IV disease, peritoneal metastasis, and serosal invasion of gastric cancer, and the high expression of Annexin A1 is an independent risk factor for poor overall survival of gastric cancer patients, which can promote the migration and invasion of gastric cancer cells. They also found that FPR1, FPR2/ALX, and FPR3 were up-regulated and increased phosphorylation of ERK1/2 and ITGB1BP1, indicating that Annexin A1 activates ERK/ITGB1BP1 signaling pathway through FPRs to induce gastric cancer cell invasion.¹⁰⁰ In gastric and colon cancer, up-regulated Annexin A1 expression is involved in cancer invasion and lymph node metastasis implicated in poor prognosis of patients.¹¹⁰

Annexin A1 and breast cancer

The expression of Annexin A1 is reduced in primary breast cancer but it is significantly elevated in metastatic breast cancer.¹⁰³ Annexin A1 is heterogeneously expressed in benign epithelium and is lost in both in situ carcinoma and invasive carcinoma, indicating a possible role for Annexin

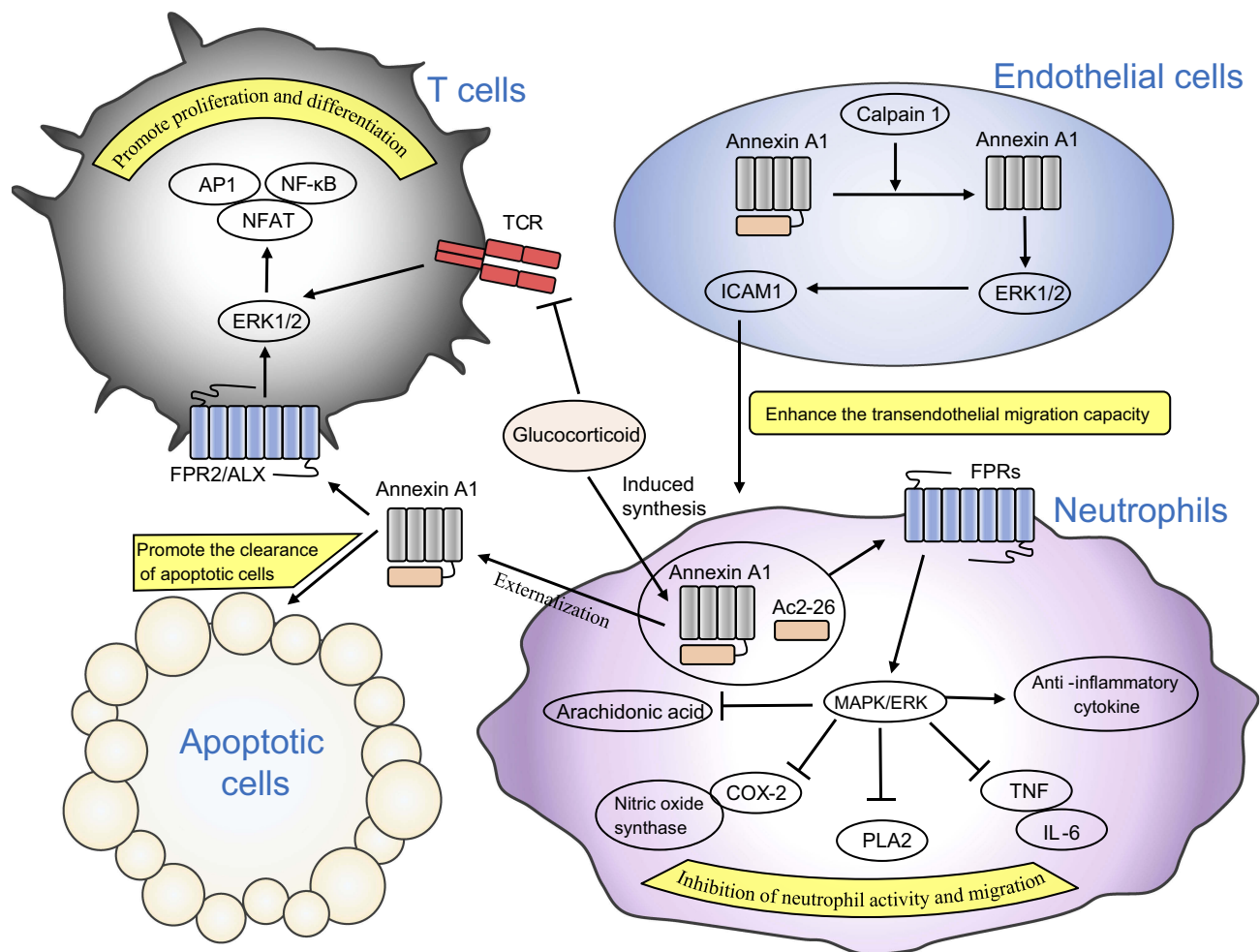


Figure 2 Mechanisms of Annexin A1 in inflammation. Annexin A1, glucocorticoid-induced synthesis in neutrophils, activates the MAPK/ERK signaling pathway through FPRs and reduces neutrophil activity to inhibit inflammatory responses. Externalization of Annexin A1 promotes clearance of apoptotic cells and stimulates T cell proliferation and differentiation, contrary to the action of glucocorticoids. ICAM1 was released through endothelial cells induced by cleaved Annexin A1 to enhance the transendothelial migration capacity of neutrophils and promote the inflammatory response.

A1 in the early events of malignant transformation.¹¹¹ Annexin A1 can induce the epithelial-to-mesenchymal transition (EMT) of tumor cells by activating the TGF β pathway, thereby enhancing the mobility and invasiveness of tumor cells in breast cancer.¹¹² Annexin A1 has the ability to increase the Smad2 phosphorylation induced by TGF β and to increase Smad3/Smad4 transcription in the MCF7 cell line, whereas the TGF β inhibitor SB-431542 can transform tumor cells back into epithelial cells. Interference of Annexin A1 in breast cancer cells reduces the metastasis of MTLn3 and 4T1 cells and impairs the TGF β /Smad signaling pathway.¹¹³ Annexin A1 is a constitutive activator of NF- κ B, which can increase the expression of MMP-9 by activating NF- κ B,¹¹⁴ thereby promoting the invasion and metastasis of breast cancer cells.^{115,116} Metastasis and invasion of breast cancer cells cause membrane damage and activate the plasma

membrane repair system, which induces the formation of Annexin A2-S100A11 complex to promote actin aggregation to repair the plasma membrane and remove the lesion membrane marked by Annexin A1.^{117–119} Epidermal growth factor receptor (EGFR) activity is closely related to breast cancer progression, and Annexin A1 and Annexin A2 are mediators of EGFR endocytosis.¹²⁰ Anti-Annexin A2 antibody can suppress EGFR tyrosine phosphorylation and endocytosis, as well as inhibit EGFR-dependent PI3K-AKT and Raf-MEK-ERK downstream pathways to reduce cell proliferation and migration.¹²¹ Anti-Annexin A2 antibody also prevents growth of human breast cancer xenograft by inhibiting neoangiogenesis.¹²² Annexin A1 also stimulates drug resistance in breast cancer cells.¹²³ Therefore, Annexin A1 may play a multifaceted role in breast cancer development, progression, and metastases.¹⁰²

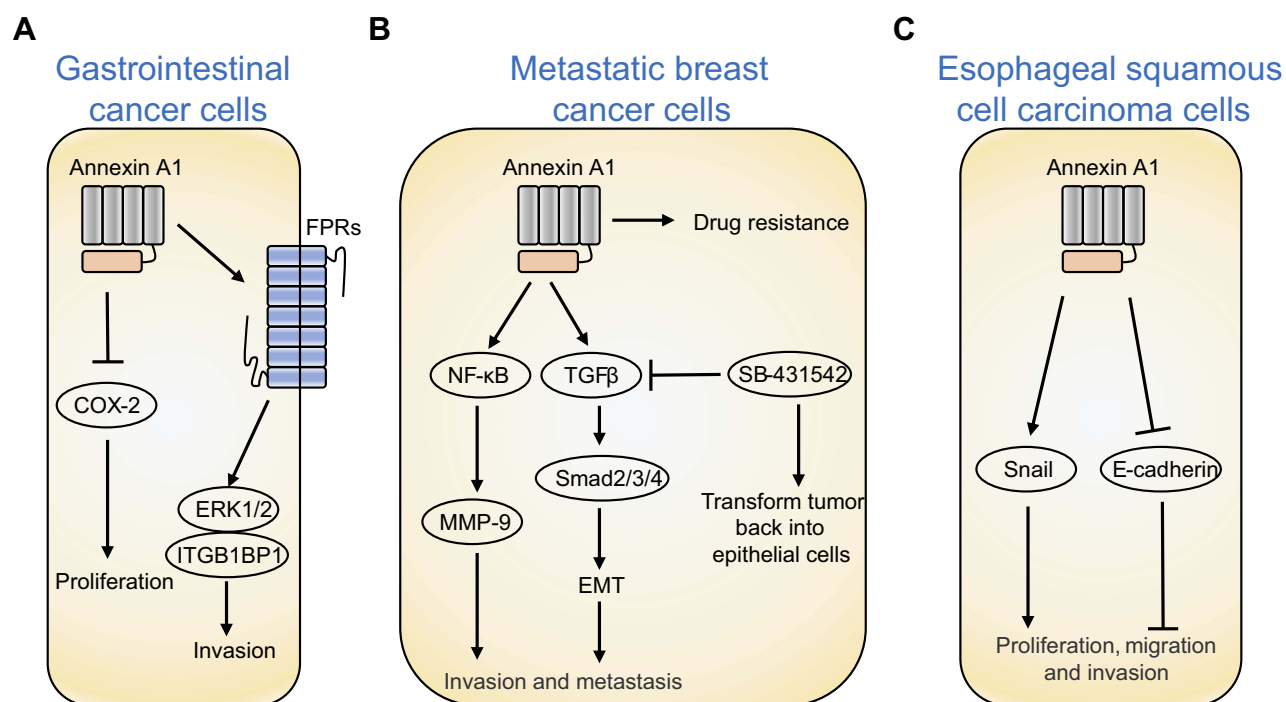


Figure 3 Mechanisms of Annexin A1 in tumorigenesis. **(A)** Annexin A1 promotes cell invasion by activating ERK/ITGB1BP1 signaling pathway through FPRs in gastrointestinal cancer cells, and Annexin A1 inhibits the activity of COX-2 to promote cell proliferation. **(B)** Annexin A1 promotes EMT through NF-κB and TGFβ signal pathway to increase invasion and migration of breast cancer cells, while TGFβ inhibitor SB-431542 can transform tumor cells back into epithelial cells. Annexin A1 also induces drug resistance in breast cancer cells. **(C)** Annexin A1 promotes cell proliferation, migration, and invasion of esophageal squamous cell carcinoma cells by promoting Snail and inhibiting E-cadherin.

Annexin A1 and esophageal cancer

The expression level of Annexin A1 is high in normal esophageal epithelium and down-regulation in esophageal squamous cell carcinoma.¹²⁴ The down-regulation of Annexin A1 was further confirmed by other groups in esophageal squamous cell carcinoma by mRNA detection and immunohistochemistry, and the increased expression of Annexin A1 is consistent with the higher degree of tumor differentiation.^{104,106} However, Wang et al found that the expression of Annexin A1 was higher in adenocarcinoma at the esophagus and esophagogastric junction.¹⁰⁵ The increased expression of Annexin A1 promotes the proliferation, migration, and invasion of esophageal squamous cell carcinoma by up-regulating the expression of Snail and down-regulating the expression of E-cadherin, indicating that Annexin A1 can regulate the metastasis and invasion of esophageal squamous cell carcinoma through the Snail/E-cadherin pathway.¹²⁵

Prospects

Annexin A1 was first identified as an anti-inflammation factor. Now, evidence showed that Annexin A1 has two-sided effects of anti-inflammatory and pro-inflammatory

through different molecular mechanisms. It is intriguing that more than 20 years of study on the roles of Annexin A1 in cancers have not provided a detailed understanding of its roles and mechanisms in various cancers, even in same cancer. Annexin A1 has been described as a “double-face” protein, because of its numerous, diverse, and sometimes opposing functions. The roles of Annexin A1 in inflammation and cancers are vacant depending on its different distribution among cytoplasm, nucleus, and cell surface. In this review, we have summarized the functional progress of Annexin A1 in inflammation and cancers, although there are not many remarkable achievements in recent years. Thus, it is urgent to further investigate the roles and mechanisms of Annexin A1 involved in inflammation and cancers, as well as other diseases to complete understanding of Annexin A1 pathophysiological involvements, which could lead to new models and therapeutic approaches in treating various diseases related to Annexin A1.

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Disclosure

The authors declare no competing interests exist in this work.

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