Chapter 3

Annexin Proteins: Novel Promising Targets for Anticancer Drug Development

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Additional information is available at the end of the chapter

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Abstract

Intracellular Ca^{2+} signaling and Ca^{2+} homeostasis have long been an important subject area of cell biology. Several intracellular Ca^{2+} binding proteins have been demonstrated until now, and among these, annexins are characterized by their ability to interact with membrane phospholipids and they form an evolutionary conserved multigene family with the members being expressed throughout animal and plant kingdoms. Annexin proteins are defined by different structural and biochemical criteria, and this multigene family has several biological features. In certain clinical conditions, the alterations on the localization or expression levels of annexin proteins are considered as the causes of pathological results and/or sequelae of disease. So, annexin proteins are indirectly linked to severe human diseases such as cardiovascular disease and cancer. Since annexin proteins are known to play roles in cancer, the researches are focused on defining the clinical significance of certain annexin proteins in cancer development and by the way anticancer treatments in the last decades. This chapter presents detailed information about annexin proteins and the studies on anticancer drug development targeting certain annexins. The studies denominate that targeting of certain annexin proteins reduces tumorigenesis and therapeutic resistance. So, annexin proteins have growing importance for anticancer drug development.

Keywords: annexin, cancer, anticancer, drug development, treatment

1. Introduction

Annexins are commonly known to be a large multigene family of Ca^{2+}-dependent phospholipid-binding proteins.They were discovered in the late 1970s and before the name "annexin", they were first introduced in diverse names which in Greek means "hold together" [1].

Over a hundred annexin proteins have been discovered in various species. Among these, 12 proteins are found in humans referred as A1–A13 (leaving A2 unassigned) [2], each having a differently positioned calcium/membrane-binding site within the core domain and a different N-terminal domain [3].

Annexins have a unique structure that allows them to locate onto membranes reversibly. They contain a conserved calcium and membrane-binding unit, which constitutes the core domain. It consists of four annexin repeats of about 70–80 amino acids. Its alfa-helical shape forms a slightly curved disc. The convex surface of it carries the calcium and membrane-binding sites as well as binding sites for phospholipids, heparin, and F-actin. The concave side on the other hand is responsible for other interactions. Ahead of the core domain comes the N-terminal region which differs in length and in sequence. It mediates regulatory interactions with protein ligands and annexin-membrane association [2]. It has been recently demonstrated that a part of N-terminal region integrates into the folded core, allowing the N-terminal region to be exposed for additional interactions upon calcium binding [4].

2. Functions of annexins

Annexins are responsible for calcium-regulated endocytotic and exocytotic events along with stabilizing organelle membranes and the plasma membrane [3]. One of the major roles of annexins is acting as scaffold proteins through calcium-regulated binding to phospholipids on the membranes. This allows the cytoplasm and the cytoplasmic side of the cell membrane to interact accordingly [5]. Mobilization of intracellular calcium triggers annexins to be recruited by cell membranes. However, some annexins can bind to membranes in the absence of calcium as well, such as annexins A9 and A10 [2].

Some annexin members specifically engage with certain sites of actin assembly at cellular membranes. For instance, the organization of raft and non-raft microdomains of smooth muscle cell membranes is regulated by annexins A2 and A6 through mediating interactions with the cytoskeleton [6].

2.1. Intracellular activities of annexins

Annexins are able to engage with cytoskeleton components reversibly. However, under certain circumstances, some annexins (A2 and A11) are found to be working together in the nucleus in the cell cycle [7]. Especially, annexin A11 plays an essential role in the terminal phase of cytokinesis. Without it, cells cannot form a midbody and hence end up in apoptosis [8]. Additionally, some annexins can be present on the cell surface. For instance, when cells are exposed to glucocorticoids, annexin A1 is found to be translocating from the cytosol to the cell surface [9]. It has also been demonstrated that annexin A2 functions as a co-receptor for plasminogen in several cell types including tumor cells, macrophages, and endothelial cells. There is also evidence that annexin A2 might be taking part in preserving vascular patency [10].

2.2. Extracellular activities of annexins

Annexins are typically known to be cytosolic proteins. However, some annexins can be found in extracellular fluids as well. There are binding sites on the outer side of cell membranes for these annexins, and they take part in several extracellular functions such as the role of annexin A5 as an anticoagulant protein, annexin A2 as an endothelial cell surface receptor for plasminogen, and the role of annexin A1 with anti-inflammatory activities on leukocytes [11]. As it is mentioned, annexin A2 functions as a receptor for plasminogen through its activities in fibrinolytic cascade as a positive modulator [12]. As a result, overexpression of annexin A2 on the surface of acute promyelocytic leukemia cells could lead to occurrence of bleeding [13].

Annexin A1 is the first member of the annexin family known to be present extracellularly. There are several findings about the extracellular activity of annexin A1. It can be found in human serum, particularly in inflammatory events such as colitis and myocard infarctus [14]. Even though annexins A1 and A4 are both present in ductal prostate epithelium cells, only annexin A1 is present extracellularly [15]. Several studies have shown that annexin A1 strongly inhibits the transendothelial migration of leukocytes, hence limiting the extent of inflammation [16].

3. Association of annexin proteins with diseases

The absence of annexin proteins can cause several abnormalities in the body. Altered expression of annexin A1 has led to a change in the inflammatory response of glucocorticoids and an increase in leukocyte migration. Additionally, it has been demonstrated that expression of other annexin proteins was affected by the loss of annexin A1 as well [17].

Recent studies have revealed that there are single-nucleotide polymorphisms (SNPs) in the genome of annexin proteins. According to studies, annexin A2 gene SNP exists in a higher level in sickle cell patients compared to control groups and is associated with osteonecrosis [18], and annexin A5 gene polymorphism has a role in recurrent pregnancy loss [19].

Annexins also take part in autoimmune diseases such as rheumatoid arthritis and type 1 diabetes. High levels of annexin V cause annexin V autoantibodies to be produced more than necessary, which may play a role in pathogenesis of these diseases [20, 21]. On the other hand, annexin A11 gene polymorphism is found to be associated with sarcoidosis, which is another autoimmune disease characterized by accumulation of epithelioid granulomas in many organs such as kidney and lungs [22].

4. Role of annexins in cancer

Annexin proteins generally exhibit diverse functions in coagulation, inflammation, signal transduction, cell proliferation, apoptosis, tumor development, angiogenesis, invasion/metastasis, and drug resistance. Several studies have revealed that annexins might be playing an important role in the process of tumor differentiation and tumor development through various mechanisms.

4.1. Annexin A1 and cancer

Annexin A1 also known as lipocortin is a member of annexin family [23], expressed in many cell types such as prostate, brain, epithelial cells, and phagocytes. It participates in various intracellular events such as cell growth, migration, cell differentiation, and mediating anti-inflammatory effects of glucocorticoids [24].

Up-regulation of annexin A1 functions as a tumor progression marker in hepatic, pancreatic, breast, and stomach carcinomas [25]. In contrast, it is down-regulated in head and neck cancers, prostate cancer, and esophageal cancers [26]. Increased annexin A1 levels have been correlated with various multidrug-resistant tumor cells as well. Annexin A1 regulates the expression of metastatic matrix metalloproteinase-9 (MMP-9) and its activity and induces the activation of NF-kB as well as promoting migration and invasion in MDA-MD-231 cells [27]. The studies have reported a significant correlation between annexin A1 levels and pathological differentiation of oral squamous cell carcinoma (OSCC) tissues [28]. According to data, the presence of annexin A1 also promotes small cell lung cancer (SCLC) cells adherence to brain endothelium leading to transendothelial migration [29]. These findings suggest that annexin A1 plays an important role in the regulation of tumor cell behavior and can be used as a potential target in breast cancer therapy.

4.2. Annexin A2 and cancer

Annexin A2, also known as Calpactin I or Lipocortin II, is a 36 kDa member of annexin family expressed by various cell types such as endothelial cells, tumor cells, and macrophages [30]. The N-terminal region of annexin A2 contains tissue plasminogen activator (tPA) [31] as well as S100A10 protein binding site [32]. On the other hand, the C-terminal region contains heparin [33], F-actin [3], and plasminogen binding sites [34].

Like the other members of annexin family, intracellular annexin A2 participates in endocytotic and exocytotic events. The down-regulation of annexin A2 inhibits cell proliferation and cell division [35], and degradation of this protein has been linked with apoptosis promoted by p53-induced pathways [36]. Annexin A2 can also function as an antioxidant. Down-regulation of annexin A2 leads tumor cells to apoptosis through pro-apoptotic p38MAPK/JNK/Akt signaling pathways upon hydrogen peroxide exposure [37].

Annexin A2 interacts with tPA which transforms plasminogen into plasmin, hence leading to extracellular matrix degradation and cell invasion. However, blocking off the surface of annexin A2 can prevent tumor cell growth and metastasis [38]. Overexpression of annexin A2 is observed in a wide range of cancer cells such as acute lymphoblastic leukemia (ALL), breast cancer, colorectal cancer (CRC), lung cancer, and many others.

In acute lymphoblastic leukemia (ALL) cells, annexin A2 has been linked with drug resistance. Experiments revealed that phosphorylated annexin A2 expression (and not annexin A2) is higher in prednisolone-resistant cells than in drug-sensitive cell lines, suggesting that preventing annexin A2 phosphorylation can bring therapeutic benefit to the treatment of drug-resistant ALL cells [39].

In pancreatic tumors, annexin A2 levels were observed to be 2- to 8-folds higher than in normal pancreas cells [40]. On the other hand, higher annexin A2 immunoreactivity is observed in lung and squamous cell carcinoma compared to control group [41]. The studies also suggest that annexin A2-dependent plasmin in human breast cancer cells may participate in angiogenesis and metastasis through ubiquitination in breast cancer tissue [42]. Recent studies have demonstrated that annexin A2 is a receptor for gastrin and progastric peptides, which are associated with growth-stimulatory effects on intestinal epithelial and colon cancer cells [43]. Annexin A2 expression is strongly correlated with disease recurrence. Hence, it could be regarded as a potential biomarker for CRC patients.

4.3. Annexin A3 and cancer

The absence of annexin A3 is believed to play an important role in drug resistance and tumor development. According to available data, there is a correlation between up-regulation of annexin A3 and increased drug resistance in ovarian carcinoma. It also increases the metastasis of lung adenocarcinoma and hepatocarcinoma. On the other hand, development of prostatic and renal carcinoma was observed with the down-regulation of annexin A3 [44].

Among digestive tract cancers, colorectal cancer (CRC) is seen very commonly. Since it bears no clinical symptoms at early stages, discovering a biomarker that will aid in diagnosis has become necessary. Annexin A3 is considered to be a potential biomarker for colorectal cancer. The higher level of annexin A3 expression has been determined in blood samples of patients with CRC, indicating the importance of annexin A3 as a biomarker in CRC [45].

4.4. Annexin A4 and cancer

Annexin A4 is a member of annexin family, also known as lipocortin IV with a size of 35.9 kDa [46]. It consists of four annexin repeats, and each region includes 5 alfa-helixes with a calcium-binding motif [47].

Annexin A4 plays an important role in membrane repair, promoting vesicle aggregation and regulation of passive membrane permeability [48]. It also takes part in calcium signaling, anticoagulation, and resistance to apoptosis [49]. Accumulated data show that annexin A4 also involves in tumor progression, invasion, metastasis, and drug resistance in various cancer types [50].

Experiments revealed that there is a positive correlation between annexin A4 and colorectal cancer progression [51]. Moreover, annexin A4 was found to be directly binding to HPA (one of the markers of CRC metastasis), which indicates that it can be considered an important marker for CRC progression [52]. Annexin A4 is also overexpressed in *Helicobacter pylori*-infected gastric cancer tissues compared to not infected ones [53]. The suggested mechanism is that *H. pylori* infection promotes gastric cancer progression through increasing annexin A4 levels in order to induce the expression of IL-8. Hence, annexin A4 can be regarded as a potential marker in gastric cancer development. The studies also showed the relation of annexin A4 with malignant mesothelioma [54], breast, laryngeal, and hepatocellular carcinoma [55, 56].

4.5. Annexin A5 and cancer

Annexin A5, also known as Endonexin II, Lipocortin V, or thromboplastin inhibitor V, plays an important role in cell membrane repair during anti-inflammatory, profibrinolytic, and anti-thrombotic activities. Intracellular annexin A5 participates in calcium channel activity on plasma membrane interacting with actin in platelets during the coagulation process [57]. On the other hand, extracellular annexin A5 plays an important role in apoptosis and phagocytosis [58].

As the most studied member of annexin family, annexin A5 also plays important role in cancer development and progression.

Experiments on tumor samples obtained from patients with hepatocellular carcinoma revealed that annexin A5 was up-regulated by 134% [59]. Hence, it could be a novel biomarker for portal vein tumor thrombus formation. Annexin A5 was also correlated with hepatocarcinoma lymphatic metastasis. Half of tumor metastasis occurs through lymphatic system leading to poor prognosis. Studies showed that in metastatic hepatocarcinoma, annexin A5 was increased by 216%, which indicates that annexin A5 levels could be used in diagnosing lymphatic metastasis of tumors [60]. Annexin A5 has been found overexpressed in human cutaneous SCC cell lines. Experiments showed that annexin A5 is mainly present in growing tumor areas [61], suggesting that annexin A5 may involve in cell proliferation and metastasis. On the other hand, knockdown of annexin A5 by siRNA decreased the invasion capability of human oral carcinoma cells while up-regulating a metastasis suppressor gene KISS-1 [62].

Annexin A5 is significantly up-regulated in pancreatic cancer cells under hypoxia condition, indicating that it may be a significant reference value in pancreatic ductal adenocarcinoma [63]. Results obtained from studies suggest that annexin A5 is involved in breast cancer since up-regulation of this protein suppressed Raf-1, MEK1/2, and ERK1/2 phosphorylation of breast cancer cells [64].

Additionally, the studies revealed that annexin A5 is also involved in cervical, colorectal, bladder carcinomas, and inflammation-associated carcinogenesis of fibrosarcoma by different mechanisms.

4.6. Annexin A7 and cancer

Annexin A7 (also known as synexin) is a member of annexin family. On human chromosome, it is located where several tumor-suppressor genes are present [65]. Although it can be found in the nucleus, it is mostly found in membranes [66].

Available data indicate that annexin A7 might function as a tumor-suppressor gene in prostate cancer, melanoma, and glioblastoma; however, it might act as a tumor promoter in gastric cancer, liver cancer, colorectal cancer, and breast cancer. Additionally, down-regulation of annexin A7 could participate in tumor invasion and metastasis [65].

5. Annexin-targeted studies

The certain members of annexin family have important functions in the development and prognosis of several carcinomas mentioned above. Thus, the studies are focused on targeting these proteins to prevent or treat the disease. The recent findings on annexin-targeted treatments are summarized hereafter.

Prostate cancer is the most common malignant cancer diagnosed in men. It accounts for 10% of all male cancers and is difficult to detect at early stages. Therefore, it is necessary to discover a novel biomarker that will aid in early diagnosis [67]. To investigate the effect of Simvastatin and annexin A10 in human PC-3 prostate cancer cells, a nude mouse tumor xenograft model was used. Simvastatin was administered with 5 and 50 mg/kg doses. According to results obtained, Simvastatin up-regulated the expression of annexin A10 which led to a significant decrease in cell proliferation, invasion, and migration as well as a reduction in tumor size. In contrast, down-regulation of annexin A10 by siRNA increased the cell proliferation, invasion, and migration in PC-3 cells. Taken together, targeting annexin A10 with statins could be used in preventing or treating prostate cancer [68].

S100 proteins are known to regulate cell functions through interacting with other proteins, particularly with annexins [69]. The interaction between annexin A2 and S100A10 plays an important role in tumor metastasis and neo-angiogenesis [70]. Therefore, inhibiting this interaction could bring therapeutic benefits in cancer treatment. Several inhibitors have been identified using biochemical screening and receptor-guided random docking techniques based on '1,2,4-triazole' structure. One of these compounds was found to be a potent inhibitor: 2-[(5-{[(4,6-dimethylpyrimidin-2-yl)sulfanyl]methyl}-4-(furan-2-ylmethyl)-4H-1,2,4-triazol-3-yl)sulfanyl]-N-[4-(propan-2-yl)phenyl]acetamide [71].

Various chemicals can cause DNA damage and mutagenesis such as As^{3+} or reactive oxygen species, and mutagenesis has an important role in cancer initiation and progression [72]. Annexin A1 is known to participate in signal transduction of growth factors and cell proliferation or differentiation. Nevertheless, in certain types of cancers, the expression of annexin A1 can be reduced such as squamous cell carcinoma, whereas it can be increased in other cancers such as bladder cancer [73]. Moreover, in some cancer cells, the expression of annexin A1 is found higher in nucleus than in cytosol, which indicates that the nuclear presence of annexin A1 could correlate with progression of certain cancers [74]. Annexin A1 requires calcium signaling and tyrosine phosphorylation in order to translocate into the nucleus. This process is triggered by DNA-damaging agents and oxidative stress [75]. Signals of damage in DNA form a mono-ubiquitinated annexin A1, which stimulates translesion DNA synthesis by heavy metals [76]. Since annexin A1 is thought to involve in responses of DNA damage and mutagenesis, the inhibition of binding activity of annexin A1 by several substances including flavonoids has been researched. Results have revealed that Quercetin, Silibinin, and Genistein inhibited the binding activity of annexin A1 in a concentration-dependent manner. Moreover, they inhibited thymidine kinase gene mutation induced by As^{3+} in lymphoma cells through

suppressing the translesion DNA synthesis which was mediated by mono-ubiquitinated annexin A1 in the nucleus [77]. These findings indicate that annexin A1 could be a novel target protein in preventing DNA damage induced by gene mutation.

Hepatocarcinoma is one of the most common malignancies with a high mortality rate and no effective treatment. A study has shown that in a mouse hepatocarcinoma cell line (Hca-P), down-regulating the expression of annexin A7 decreases the proliferation and induces apoptosis [78]. To investigate the role of it further, an experiment targeting annexin A7 has been performed. In order to down-regulate the expression of annexin A7, an RNA interference technique (RNAi) was used to demonstrate the changes in cell viability where annexin A7 levels are altered after Cisplatin treatment. According to data obtained, following the down-regulation of annexin A7, treatment with Cisplatin reduced the proliferation of Hca-P cells significantly and induced apoptosis. Additionally, altering the expression of annexin A7 decreased the expression of Bcl2 and increased the expression of caspase-3 and cytochrome-C, which indicates that presence of annexin A7 inhibits apoptosis through the mitochondrial pathway [79] (see **Figure 1**).

Annexin A1 is known to participate in the process of inflammation along with a wide range of cellular activities [2]. It has been revealed that annexin A1 plays a role in the process of apoptosis in inflammatory cells as well [80]. Experiments have shown that elevated annexin A1 levels in U937 cells and bronchoalveolar epithelial cells induce apoptosis through caspase-3 activation [81]. Moreover, it has been shown that in thyroid cancer cells, apoptosis induced by TRAIL is also mediated through annexin A1 expression [82]. Additionally, in

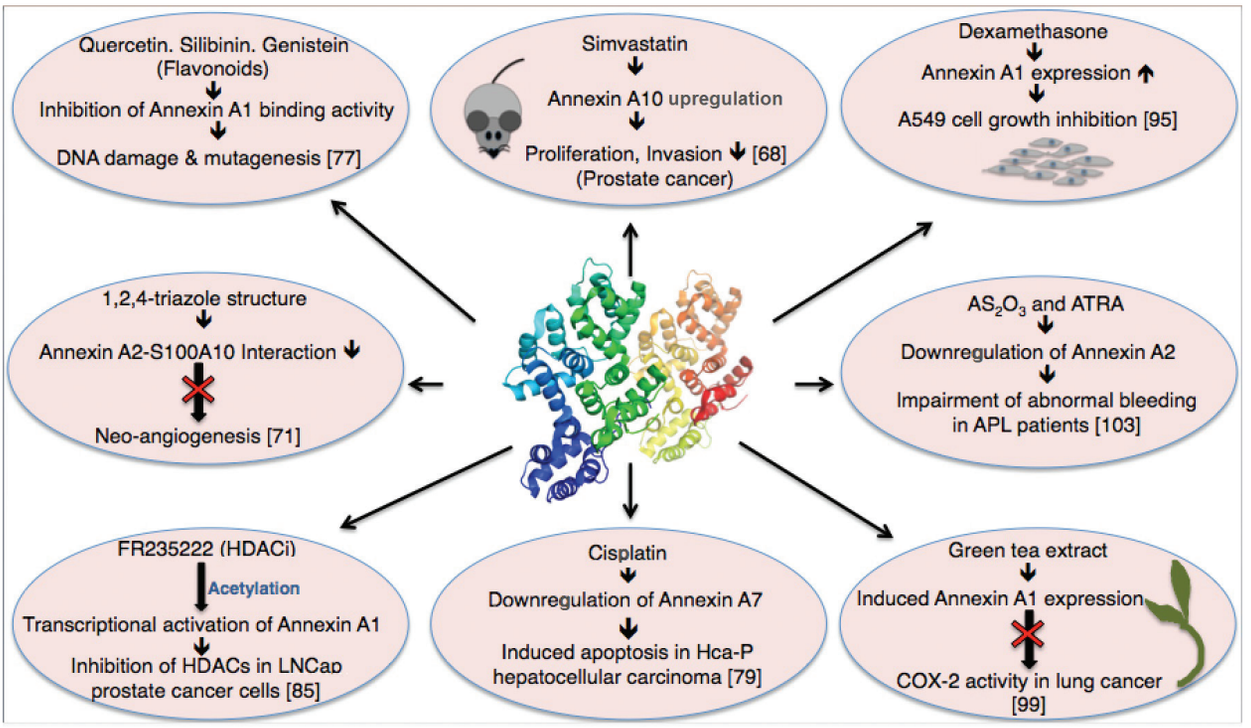

Figure 1. Schematic representation of annexin-targeted novel studies (the centered protein figure was prepared by Pymol Educational Program using annexin IV protein (PDB ID: 2ZOC) from Protein Data Bank).

prostate cancer cells, down-regulation of annexin A1 has been suggested to contribute in cancer initiation and progression [83]. On the other hand, up-regulation of annexin A1 has decreased the cell viability and induced apoptosis through caspase activity [84], which indicates that annexin A1 could be taken as a tumor-suppressor protein in prostate cancer cell line (LNCaP).

Experiments have shown that the expression of annexin A1 decreases in prostate cancer cells. Therefore, the mechanism of this reduction has been investigated. The fact that annexin A1 levels only decrease and are not completely eliminated brings the possibility that dysregulation of annexin A1 occurs at the level of gene transcription [85]. It has been proposed that deacetylation of histone proteins leads to altered gene expressions [86]. The turnover of histone acetylation is mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). These enzymes can induce and inhibit transcription [87], and they show dysregulated activities in human cancers leading to neoplastic transformation of tumor cells [88]. Hence, the balance of HAT/HDAC has been a target in cancer therapy. Various compounds have shown antitumor effects through inhibiting HDACs such as valproic acid and some cyclic peptides (FK228) [89].

Recently, a novel compound, FR235222, with inhibitory effect on histone deacetylases has been isolated from a fungus [90]. Experiments have revealed that FR235222 induces apoptosis and regulates annexin A1 expression in leukemia cell lines. The possible mechanism suggested was that reduced levels of annexin A1 could be mediated by deacetylation of histone proteins [85]. To confirm this hypothesis, the effect of FR235222 on apoptosis and annexin A1 expression has been studied in prostate cancer cell lines (LNCaP). Western blotting results have shown that FR235222 induces the expression of annexin A1 in a time-dependent manner with a peak at 48 h. Also, experiments with actinomycin D indicated that the increase of annexin A1 was at transcription level. In contrast, when annexin A1 expression was down-regulated by siRNA transfection protocol, a partial decrease in FR235222-induced apoptosis has been observed by 26% and in caspase-3 activity by 22% in LNCaP cells [91]. These findings suggest that transcriptional activation of annexin A1 is induced by FR235222 through acetylation of histone proteins and inhibition of HDACs in LNCaP cells, and the increased levels of annexin A1 lead to apoptosis through caspase activity.

Lung cancer is one of the most common cancer types with a high rate of mortality [92]. Studies have shown that inflammation participates in the development of lung cancer. One of the components of inflammatory pathways is the COX-2/PGE_2 pathway. Increased expression of COX-2 is often seen in human non-small cell lung cancer (NSCLC). This leads to overexpression of PGE_2 which involves in various cancer-related activities such as resistance to apoptosis, angiogenesis, invasion, and metastasis [93]. Annexin A1 acts as a phospholipase A2 inhibitor and is associated with several functions such as cell differentiation, cell growth arrest, and anti-inflammation [94]. The effect of annexin A1 in human NSCLC cell line (A549) has been investigated. Studies have concluded that Dexamethasone increased the expression of annexin A1 in A549 cells which inhibited cell growth [95]. In contrast, gene deletion of annexin A1 led to an excessive inflammatory stimuli characterized by increased leukocyte migration and IL-1B generation [17].

Green tea (*Camellia sinensis* leave extract) is known to contain polyphenols which are natural antioxidants. Accumulated data have shown that green tea exhibits a protective role against various cancers including lung cancer [96]. It has been observed that green tea extract (GTE) induced annexin A1 in human urothelial cells and in lung cancer (A549) cells in a dose-dependent manner [97]. Moreover, GTE-induced annexin A1 also mediated cytoskeletal actin remodeling, which led to an increase in cell adhesion and decrease in cell motility. Additionally, inhibition of COX-2 and PGE2 was observed in NSCLC cell lines following GTE-induced annexin A1 expression. In contrast, silencing annexin A1 expression overturned the inhibitory effect of GTE on COX-2. These results suggest that GTE shows its effect through inducing annexin A1 expression, therefore targeting annexin A1 could be a promising mechanism in preventing lung cancer [98].

Annexin A2 is present in various cell types including endothelial cells, neuronal cells, and cancer cells. It acts as a co-receptor for plasminogen and tissue plasminogen activator (tPA) [99]. In acute promyelocytic leukemia (APL) cells, annexin A2 is found to be overexpressed. This causes plasmin to be highly produced leading to hyperfibrinolysis and then abnormal bleeding in patients [100]. A study has been performed to investigate the regulation of annexin A2 expression in APL cells as well as the effect of arsenic trioxide (As_2O_3) and all-trans retinoic acid (ATRA). Results have shown that annexin A2 is expressed abnormally on the surface of APL cells. Additionally, it has been observed that annexin A2 exhibits a unique activity of binding the tPA substrate plasminogen leading to enhanced plasminogen activity in APL cells [101]. Following the administration of As_2O_3 and ATRA in patients with APL, the expression of annexin A2 was significantly down-regulated on the surface of APL cells compared to the control group. Bleeding started to disappear a week after the treatment with ATRA and As_2O_3 as well as parameters of fibrinolysis [102]. These findings suggest that targeting annexin A2 could help treat the abnormal bleeding in patients with APL.

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