Research progress of cPLA2 in cardiovascular diseases (Review)

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Abstract. Cytoplasmic phospholipase A2 (cPLA2) is a vital member of the PLA2 family. Studies have demonstrated that cPLA2 plays a key role in various inflammatory-related diseases and cancers. However, limited research has focused on cPLA2 in cardiovascular diseases. The present review discussed and summarized the research progress on cPLA2 in atherosclerosis, cardiomyopathy, myocardial ischemia-reperfusion injury and other related conditions. It also highlighted the critical molecular mechanisms by which cPLA2 regulates the pathophysiological processes of vascular endothelial cells, platelets and myocardial cells in cardiovascular diseases. Current studies confirm that cPLA2 plays an important role in cardiovascular diseases and has the potential to become a therapeutic target for the diagnosis, treatment evaluation and prognosis of these conditions. The present review systematically explored the significant role of cPLA2 in cardiovascular diseases and elaborated on its underlying molecular mechanisms. The findings aimed to refine the theoretical understanding of cardiovascular disease pathogenesis and provide a foundation for developing novel treatment strategies.

Contents

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1. Introduction

Cytoplasmic phospholipase A2 (cPLA2; Fig. 1) belongs to the lipolytic enzyme family and hydrolyzes the ester bond at the sn-2 position of phospholipids, generating free fatty acids and lysophospholipids. Members of the PLA2 family are classified into six subfamilies based on their location in the body, substrate specificity and physiological functions: Secretory PLA2s (sPLA2s), cPLA2s, Ca^{2+}-independent PLA2s (iPLA2s), platelet-activating factor acetylhydrolase PLA2s (PAF-AH PLA2s), lysosomal PLA2s (LPLA2s) and adipose tissue-specific PLA2s (AdPLA2s). Among these, cPLA2s play a crucial role in inflammatory diseases, cerebral ischemia-reperfusion injury, hypertension and autoimmune diseases (1-4).

cPLA2, a member of the PLA2 family, is a single-subunit protein composed of 749 amino acids with two functional domains: the Ca^{2+}-dependent lipid-binding (CaLB) domain, also known as the C2 domain and the catalytic active region (CAT), connected by flexible hinges. cPLA2 primarily acts on the phospholipid bilayer of cell membranes to catalyze the release of free arachidonic acid (AA) (5). cPLA2 is activated through two primary pathways: The Ca^{2+}-dependent pathway, when intracellular Ca^{2+} levels rise, Ca^{2+} binds to the C2 domain of cPLA2, facilitating its translocation from the cytoplasm to the membrane's phospholipid matrix; the phosphorylation pathway, when phosphorylation of amino acid residues in the hinge region between the C2 domain and the catalytic domain enhances the binding affinity and catalytic efficiency of cPLA2. This phosphorylation induces conformational changes, bringing the catalytic domain closer to the substrate. Ultimately, cPLA2 on the phospholipid membrane catalyzes phosphatidylinositol hydrolysis, promoting AA release (6,7). AA, an essential fatty acid, can be metabolized into various bioactive substances, including prostaglandins, platelet-activating factors and leukotrienes, which regulate pathophysiological processes such as inflammation, cell proliferation, apoptosis

and platelet aggregation (8,9). cPLA2 has been shown to participate in essential cellular processes, including phospholipid metabolism, signal transduction and membrane remodeling under physiological conditions (1,10,11). However, increased cPLA2 activity and excessive AA release, along with pro-inflammatory mediators, can compromise lysosomal membrane integrity, exacerbating inflammation and oxidative stress under pathological conditions (12). Numerous studies have confirmed the involvement of cPLA2 in the pathogenesis of various diseases. However, systematic summaries of its role in cardiovascular diseases and underlying mechanisms remain limited. Existing evidence indicates that cPLA2 plays a pivotal role in the development of cardiovascular conditions, including atherosclerosis, myocardial ischemia-reperfusion injury and hypertension (3,4,13) (Table I). This review highlighted the functional significance and potential mechanisms of cPLA2 in cardiovascular diseases, offering novel insights into their diagnosis and treatment.

2. cPLA2 exacerbates inflammation

cPLA2 promotes the production and release of inflammatory mediators. Tissue damage and oxidative stress can activate cPLA2, which hydrolyzes the sn-2 site of membrane phospholipids to produce metabolites, primarily AA and lysophospholipids. These metabolites, in turn, generate downstream molecules such as leukotrienes, prostaglandins, lipoxin A, thromboxane, sphingomyelin and lysophosphatidic acid via cyclooxygenase (COX) and lysophospholipase activity. These molecules trigger inflammatory responses and oxidative stress, resulting in a robust inflammatory cascade (14).

cPLA2 activates the inflammatory signal conduction pathway. Key signaling pathways such as NF-κB and MAPKs play critical roles in cell signal transmission, regulating processes such as inflammation, immune responses, cell proliferation and apoptosis. Studies have confirmed that cPLA2 activates these inflammatory signaling pathways (1,15-18) (Fig. 2).

NF-κB signaling pathway. NF-κB is a classical transcription factor that regulates the expression of multiple genes by translocating from the cytoplasm to the nucleus. It serves as a key regulator of inflammatory responses, influencing both the progression and resolution of inflammation. AA released by activated cPLA2 acts as a second messenger, participating in downstream signaling activation. AA is catalyzed by COX into prostaglandin H2 (PGH2), which is subsequently converted into prostaglandin E2 (PGE2). PGE2 activates G protein-coupled receptors (GPCRs) on cell membranes, triggering downstream signaling events such as the phosphorylation and degradation of IκB (inhibitor of NF-κB). The degradation of IκB releases active NF-κB, promoting its nuclear translocation and binding to specific DNA sequences to initiate the transcription of downstream genes. Excessive activation of cPLA2 can prolong NF-κB activity, leading to sustained inflammatory responses and tissue damage (15-17).

MAPKs signaling pathway. Mitogen-activated protein kinases (MAPKs) represent a highly conserved cell signal transduction pathway that conveys extracellular and intracellular signals to regulatory networks through phosphorylation of key protein targets. The primary components include ERK1/2, JNK and p38 MAPK (18). The MAPKs pathway can be activated by various exogenous stimuli, such as growth factors, stress and inflammatory factors, or endogenous stimuli, such as cellular stress and DNA damage. Stimulation leads to the activation of receptors, such as receptor tyrosine kinases and GPCRs, which subsequently activate MAP3K through a series of downstream kinase cascades. MAP3K phosphorylates MAP2K, which, in turn, activates MAPK. This process triggers the activation of nuclear transcription factors, ultimately regulating cellular physiological functions (19). cPLA2 activates the MAPKs signaling pathway through several mechanisms. Diacylglycerol, generated by cPLA2-catalyzed phosphatidylinositol 2 (PIP2), directly activates protein kinase C, which then stimulates the MAPKs pathway (20). Additionally, AA, a product of cPLA2 catalysis, plays a crucial role in the MAPKs network. AA activates ERK, JNK and p38 MAPK, influencing processes such as cell proliferation, apoptosis and differentiation. Among these, p38 MAPK primarily mediates inflammatory responses and cellular stress (18,21). In summary, cPLA2 serves as a key upstream molecule in the activation of MAPKs signaling pathways.

The PI3K/Akt signaling pathway. cPLA2, as a phosphatidylinositol-specific phosphoesterase, activates the PI3K/Akt signaling pathway through multiple mechanisms. It promotes this pathway by inducing the production and release of growth factors. For instance, cPLA2 facilitates the secretion of TNF-α, which activates the PI3K/Akt pathway (21). Moreover, cPLA2 enhances PI3K activity by regulating phosphatidylinositol content in cell membranes, thereby increasing the affinity of PI3K (22-24). Additionally, cPLA2 directly activates Akt by promoting its phosphorylation and enhancing its activity, which further drives the PI3K/Akt signaling pathway (25).

3. cPLA2 participates in platelet activation

A number of studies have demonstrated that cPLA2 plays a pivotal role in platelet activation. Platelet activation, typically induced by external stimuli such as cytokines or vascular damage, triggers intracellular signaling pathways that activate cPLA2, leading to the release of AA. In platelets, AA is primarily metabolized by COX-1 into PGH2, which is subsequently converted into thromboxane A2 (TXA2) (26). TXA2 promotes platelet activation and vasoconstriction (27). Upon activation, platelets release bioactive substances such as platelet factor 4, platelet-derived growth factor and ADP. These substances stimulate neighboring platelets, enhancing adhesion and aggregation. Additionally, activated platelets expose receptors, including GPIIb/IIIa and GPIb/IX, on the endothelial surface. These receptors bind to molecules such as fibronectin and von Willebrand factors, exposed during vascular injury, further facilitating platelet aggregation and the formation of platelet thrombi (28,29). PI3K/Akt and MAPK pathways are the two major signaling pathways involved in platelet activation and aggregation. The PI3K/Akt pathway is activated by various platelet agonists, including thrombin, collagen and ADP, promoting platelet activation, granule release and integrin activation. Similarly, the MAPK pathway is activated by platelet agonists and regulates genes involved in platelet functions, such as integrin and TXA production, thereby enhancing platelet activation and aggregation (30,31).

Table I. Roles and mechanisms of cPLA2 in various cardiovascular diseases.

Cardiovascular diseases	cPLA2-related pathogenic mechanisms	(Refs.)
Atherosclerosis	Inflammatory responses and oxidative stress lead to increased vascular permeability, while the proliferation and migration of smooth muscle cells contribute to plaque formation and vascular remodeling. Excessive cell apoptosis results in endothelial cell damage, accompanied by a blockade of autophagy flux, which causes the accumulation of harmful substances and damaged organelles.	(13,28,29,32-35, 56-60)
Coronary artery disease	Inflammatory responses provoke plaque instability and rupture, coupled with platelet activation that causes platelet aggregation and thrombus formation.	(28,60)
Myocardial infarction	Inflammatory responses and oxidative stress inflict damage on myocardial cells. This is exacerbated by excessive cell apoptosis during reperfusion injury and platelet activation, which together promote plaque and thrombus formation. The process is further complicated by a blockade of autophagy flux, leading to the accumulation of harmful substances and damaged organelles.	(28,29,32-35, 56-60)
Heart failure	The damage to myocardial cells from inflammatory responses and oxidative stress necessitates myocardial remodeling, involving cell apoptosis, myocardial fibrosis and hypertrophy. This scenario is compounded by the blockade of autophagy flux, resulting in the accumulation of harmful substances and damaged organelles.	(32-35,56-60)
Hypertension	Inflammatory responses and oxidative stress cause endothelial dysfunction through inflammatory mediators, with subsequent vasoconstriction regulated by sodium and calcium channels. This leads to arteriosclerosis, which narrows blood vessels and is regulated further by the renin-angiotensin system.	(13,67,74)
Cardiac valve disease	Inflammatory responses and oxidative stress lead to the destruction and proliferation of valve tissue. This promotes valve cell proliferation and migration, resulting in the thickening, calcification and fibrosis of the valves.	(1,32-34,75)

cPLA2, cytoplasmic phospholipase A2.

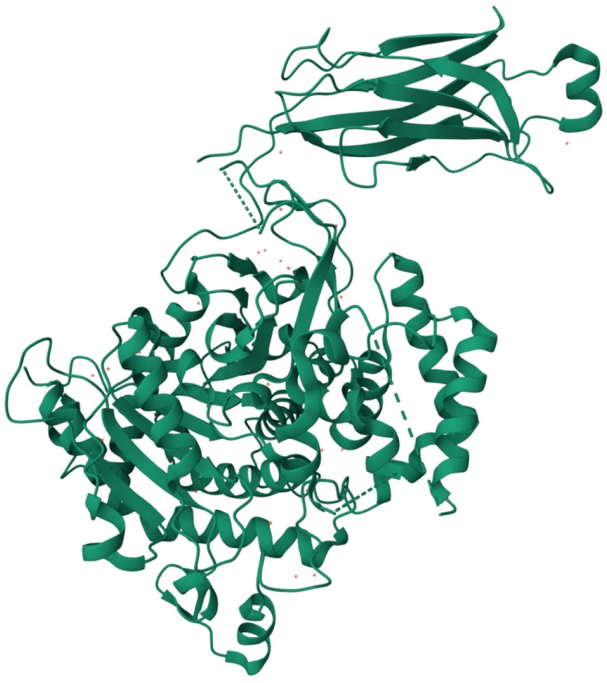

Figure 1. The molecular structure of cytoplasmic phospholipase A2. It reveals a free canonical octamer (data from https://www.rcsb.org/3d-view/1CJY).

In summary, cPLA2 is a critical regulator of platelet activation, functioning through its involvement in the PI3K/Akt and MAPK signaling pathways.

4. cPLA2 regulates myocardial cell apoptosis

In the study of cell death, several mechanisms have been recognized, including apoptosis, necroptosis, pyroptosis and ferroptosis. These mechanisms play critical roles in both physiological and pathological cellular processes (32). cPLA2 plays a pivotal regulatory role in cell death by catalyzing the hydrolysis of cell membrane phospholipids to generate arachidonic acid and its metabolic products (33). In necroptosis, cPLA2 facilitates membrane remodeling and the release of necrotic signals by regulating lipid metabolism and altering cell membrane structure (34). In pyroptosis, cPLA2 activates the synthesis of pro-inflammatory cytokines, such as IL-1β and IL-18, by releasing AA, which further promotes inflammasome formation and triggers the pyroptotic response (35). Additionally, during ferroptosis, cPLA2 modulates membrane lipid peroxidation, influencing oxidative damage to membrane lipids and the metabolism of intracellular iron, thereby indirectly regulating ferroptosis (36). The present review focused on the critical role of cPLA2 in apoptosis, specifically its

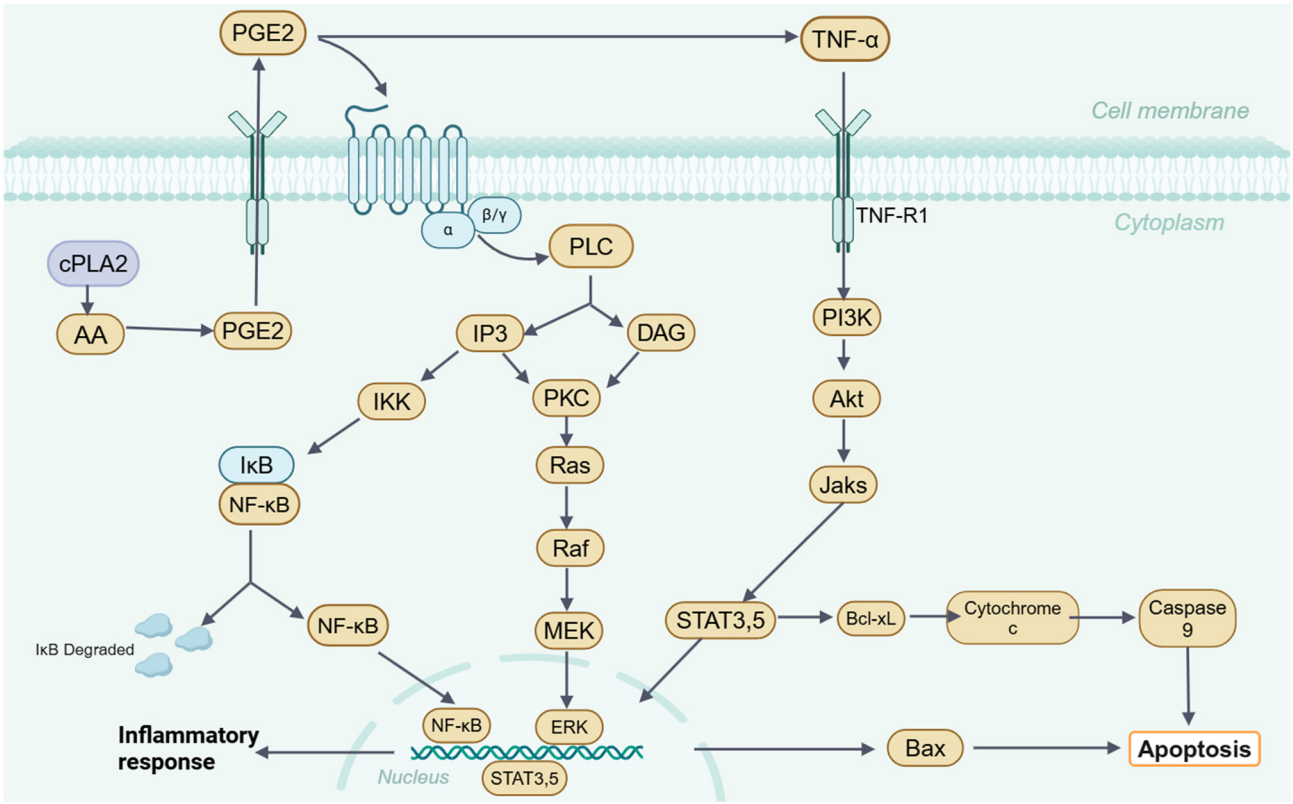

Figure 2. cPLA2 mainly participates in cardiovascular diseases through regulating relative signaling pathways. i) cPLA2 exacerbates inflammation by promoting the production and release of inflammatory mediators and activating inflammatory signaling; ii) cPLA2 regulates myocardial cell apoptosis and platelet activation; iii) cPLA2 modulates these processes primarily through NF-κB, MAPKs and PI3K/AKT signaling. cPLA2, cytoplasmic phospholipase A2; PGE2, prostaglandin E2; PKC, protein kinase C; DAG, diacylglycerol; PLC, phospholipase C; AA, arachidonic acid.

regulation of the multiple signaling pathways involved in this process.

Apoptosis is the most well-studied and classical form of programmed cell death, crucial for maintaining normal tissue structure and function. Excessive apoptosis of myocardial cells results in significant cell loss, leading to myocardial tissue depletion and impaired blood supply to the affected area (37,38). This process triggers cardiac fibrosis, where healthy myocardium is replaced by fibrous connective tissue. Fibrosis renders the heart stiff, reduces its elasticity and causes ventricular dilation. These changes exacerbate cardiac remodeling, further impairing cardiac function and leading to alterations in the overall structure of the heart (39). Excessive apoptosis has been implicated in myocardial ischemia, ischemia/reperfusion injury, post-ischemic cardiac remodeling and the progression of cardiovascular conditions such as coronary atherosclerosis, myocardial infarction, hypertension and heart failure (40-44). The following paragraphs elaborate on these processes (Fig. 2).

MAPKs signaling. cPLA2 and MAPK signaling pathways are closely linked in the regulation of cell apoptosis. cPLA2 participates in the metabolism of PIP2 on the cell membrane, converting it into phosphatidylinositol triphosphate (PIP3) (2). PIP3 plays a crucial role in the apoptotic process. cPLA2 activates PI3K through PIP3, which subsequently activates MAPKKK, further stimulating the MAPK signaling pathway (41). The MAPK signaling pathway promotes apoptosis in various cell types, including cardiomyocytes, endothelial cells, macrophages and tumor cells, through different subtypes (such as JNK, p38 MAPK and ERK). Activated JNK and p38 MAPK enhance the expression of apoptosis-related transcription factors (such as p53) and increase pro-apoptotic genes (such as Bax), while simultaneously downregulating anti-apoptotic factors such as Bcl-2) (42,45). In cardiomyocyte apoptosis, distinct MAPK members may have varying roles (46). JNK activation regulates cell apoptosis by either stimulating apoptotic factor expression or inhibiting anti-apoptotic mechanisms. For instance, JNK activates the transcription factor c-Jun, promoting the expression of apoptosis-related genes, including apoptotic proteins and mitochondrial regulatory factors, ultimately leading to cell apoptosis in cardiomyocytes (47). However, JNK activation may act as an anti-apoptotic factor in cardiomyocytes derived from embryonic stem cells (48). Under pathological conditions such as ischemia-reperfusion, inflammation and oxidative stress, p38 activation increases mitochondrial membrane permeability and caspase enzyme activation, thereby promoting myocardial cell apoptosis (49). ERK, through a series of cascade reactions, plays a protective role in myocardial cell apoptosis. ERK activation inhibits cardiomyocyte apoptosis by upregulating the Bcl-2/Bax ratio through downregulation of Bax expression, thereby maintaining mitochondrial stability (50). In summary, cPLA2 regulates myocardial cell apoptosis by activating different members of the MAPK signaling pathway.

PI3K/Akt signaling. The PI3K/Akt signaling pathway plays a crucial role in regulating cell survival and apoptosis, primarily through its control of anti-apoptotic mechanisms. Dysregulation of this pathway is closely associated with the onset and progression of various diseases, particularly cancer, neurodegenerative disorders and cardiovascular diseases (51,52). Akt is the primary effector kinase, regulating cell survival and apoptosis by phosphorylating a series of downstream target proteins. Akt reduces the pro-apoptotic effects of factors such as Bad and Bax by phosphorylating and inhibiting them. It also phosphorylates and activates anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, thereby enhancing cell survival (53). The PI3K/Akt signaling pathway is essential for the normal physiological functions of cardiomyocytes and is closely related to cardiomyocyte apoptosis. Dysregulation of this pathway can lead to cardiomyocyte apoptosis, contributing to cardiovascular diseases, including myocardial infarction and heart failure (52). Activation of the PI3K/Akt pathway promotes myocardial cell survival and inhibits apoptosis (49). The PI3K/Akt pathway regulates the release of AA and associated apoptosis processes by inhibiting cPLA2 activity. Activated Akt directly phosphorylates and inhibits cPLA2, reducing AA production (43). Additionally, Akt can regulate cPLA2 activity by preventing its translocation to the cell membrane, a critical step in AA release. Akt signaling disrupts this process, thereby decreasing AA production. However, under certain pathological conditions, such as myocardial ischemia, injury, or hypertrophy, the PI3K/Akt signaling pathway is inhibited. This inhibition weakens the effect of Akt on cPLA2, potentially leading to cPLA2 activation, increased AA release and enhanced cell apoptosis (54).

NF-κB signaling. As aforementioned, cPLA2 activates the NF-κB signaling pathway by producing AA and its metabolites. This pathway promotes cell apoptosis by regulating the expression of apoptotic factors. NF-κB induces FasL expression, initiating apoptotic signaling and promoting cell apoptosis. It may also increase the production of TNF-α, which activates downstream apoptotic signals, including Caspase-8, to initiate apoptosis (44). Additionally, NF-κB accelerates cell apoptosis by regulating p53, further exacerbating cardiac damage (55). These mechanisms play a significant role in various cardiovascular diseases, including heart failure and coronary artery disease (56). For example, NF-κB mediates atherosclerosis through several key mechanisms: First, it promotes endothelial cells to express pro-inflammatory molecules, recruiting and activating inflammatory cells to enhance local inflammation. Second, NF-κB affects the proliferation and migration of smooth muscle cells, contributing to plaque formation. It also increases oxidative stress, leads to endothelial injury and promotes the formation of foam cells through the accumulation of cholesterol and lipids. These processes collectively promote the development of atherosclerosis (13,56).

5. cPLA2 participates in the autophagy flux

Autophagy is a process of cellular self-degradation that maintains cellular homeostasis by degrading and recycling harmful or aging components, allowing cells to adapt to environmental changes (57). This process involves three main stages: Activation, transportation and degradation. Specifically, it includes the formation of phagophores, the development of autophagosomes, the fusion of autophagosomes and lysosomes to form autolysosomes and the subsequent degradation of substrates within them (58). This entire process is referred to as autophagic flux. Studies have shown that autophagy plays a crucial role in various cardiovascular diseases. The heart is a highly metabolically active organ with significant demands for oxygen and energy. Under conditions such as ischemia, reperfusion injury, or other pathological states, autophagy can be activated to meet energy needs, reduce oxidative stress, inhibit cell apoptosis and maintain cellular homeostasis, thereby protecting the heart from damage (59,60). In heart diseases such as myocardial infarction and heart failure, autophagic flux is often inhibited or impaired. This abnormal autophagic activity leads to the accumulation of harmful substances and damaged organelles within myocardial cells, further exacerbating cell damage (61,62). Additionally, studies using acute hemodynamic stress models have shown that excessive autophagy can result in increased myocardial cell hypertrophy, impaired cardiac performance and the activation of cardiac stromal cells (such as fibroblasts), promoting fibrosis. These mechanisms suggest that excessive autophagy can have pathological consequences, potentially contributing to cardiac hypertrophy and heart failure (63,64). Furthermore, autophagic flux dysfunction can reduce endothelial cell tolerance to oxidative stress and inflammatory responses, leading to the accumulation of oxidized LDL (low-density lipoprotein) and promoting the formation and progression of atherosclerosis. Excessive autophagy may also increase cell apoptosis within plaques, compromising their structural stability and making them more prone to rupture, thereby triggering cardiovascular events (65). Studies have demonstrated that cPLA2 can regulate autophagic flux through multiple pathways, contributing to various cardiovascular diseases (49,66-75) (Fig. 3).

cPLA2 inhibits the expression and activity of autophagy-related proteins. In the early stages, when cells are exposed to stress, nutrient deprivation and insufficient oxygen supply, autophagy is activated (66). These signals include the inhibition of mTOR complex 1 (C1), activation of AMPK and an increase in intracellular calcium ion concentration (67,68). The Unc-51-like kinase 1 (ULK1) complex, which consists of proteins such as ULK1, focal adhesion kinase family interacting protein of 200 kDa, autophagy-related 13, autophagy-related 101, as well as the Beclin-1-VPS34 complex (including Beclin-1, VPS34 and other auxiliary proteins), are activated (46,69). These complexes interact to regulate downstream autophagic processes. cPLA2 hydrolyzes phosphatidylcholine and phosphatidylethanolamine to produce free fatty acids, which promote the accumulation of intracellular phosphatidic acid (PA). The accumulation of PA can activate mTORC1, which inhibits the activity of the ULK1 complex and reduces the formation of the Beclin-1-VPS34 complex, ultimately inhibiting autophagy. Additionally, cPLA2 can reduce the expression of Beclin-1 by inhibiting the PI3K/Akt signaling pathway, further suppressing autophagy (67-71).

cPLA2 reduces the formation of autophagosome. After the initiation phase, autophagic vesicles begin to form. These

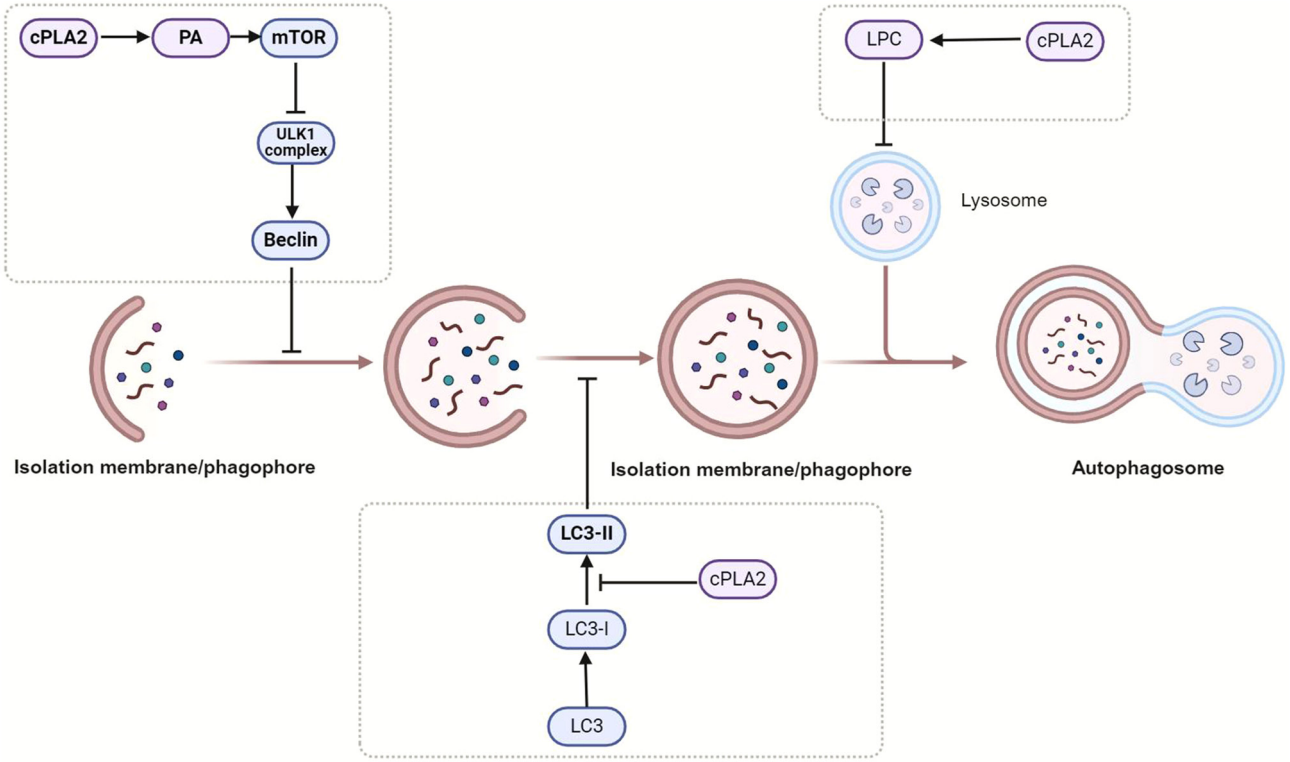

Figure 3. Main mechanisms of cPLA2 in regulating autophagy flow. i) cPLA2 inhibits the expression and activity of autophagy-related proteins; ii) cPLA2 reduces the formation of autophagosomes; iii) cPLA2 blocks autophagy by disrupting the integrity of lysosomal membranes. cPLA2, cytoplasmic phospholipase A2; LPC, lysophosphatidylcholine; ULK1, unc-51 like autophagy activating kinase 1; LC3, microtubule-associated protein 1 light chain 3; mTOR, mechanistic target of rapamycin kinase; PA, phosphatidic acid.

vesicles consist of a double membrane that engulfs cellular components to be degraded. This process involves multiple autophagy-related proteins, such as ATG9, ATG16L1 and the ATG5-ATG12 complex (66,71). These proteins promote the formation and expansion of autophagic vesicles through interactions and phosphorylation. The vesicles close in a single step to form autophagosomes. This process involves the lipidation of LC3, wherein LC3-I is converted to LC3-II, which binds to the inner membrane of the autophagic vesicle, promoting the formation and closure of the autophagosome. The activation of cPLA2 can influence the composition of membrane phospholipids, thereby affecting the lipidation of LC3 proteins and their binding to the autophagosome membrane. A study showed that inhibiting cPLA2 can promote the accumulation of LC3-II (the phosphorylated form of LC3), thereby increasing autophagosome formation (49).

cPLA2 blocks autophagy by destroying the integrity of lysosomal membranes. After the formation of the autophagosome, it fuses with lysosomes to form autophagic lysosomes (autolysosomes). The components and organelles within the autophagosome are degraded by hydrolytic enzymes in the autolysosome, facilitating the recovery and reuse of intracellular components to meet the energy needs of the cell and synthesize new biomolecules (57). cPLA2 is primarily responsible for the sn-2 hydrolysis of membrane phospholipids on the cell membrane, generating inflammatory mediators such as lysophospholipids and AA. Lysophospholipids are a class of phosphatidylinositol metabolites and important cell signaling molecules, including lysophosphatidylcholine, lysophosphatidylethanolamine and lysophosphatidylserine, among others (72). These lysophospholipids can increase lysosomal membrane permeability by disrupting the integrity of the autolysosome or regulating ion channels, which further disrupts the fusion of autophagosomes with lysosomes, leading to a blockade of autophagic flux (49,73,74). Fusion disorders between the autophagosome and lysosome result in impaired degradation of cellular components, promote the transcription of inflammatory factors and exacerbate cell apoptosis (75).

6. The effective role of cPLA2 in cardiovascular diseases.

The preceding section detailed the potential mechanisms of cPLA2. Below, these mechanisms are associated with clinical significance in cardiovascular diseases, summarizing the research progress of cPLA2 in these conditions.

Atherosclerosis. Atherosclerosis is the underlying pathology of cardiovascular diseases (76) and cPLA2 plays a significant role in this process.

Amplifying inflammatory response. The formation of atherosclerosis is closely associated with chronic low-grade inflammation (77) and cPLA2 promotes the synthesis of inflammatory mediators, such as prostaglandins and leukotrienes. These inflammatory mediators activate endothelial cells, induce the recruitment of leukocytes and macrophages and initiate local inflammatory responses. Persistent inflammation

promotes lipid accumulation in the arterial wall and accelerates plaque formation (56).

Promoting smooth muscle cell proliferation and migration. cPLA2 also promotes the proliferation and migration of smooth muscle cells by regulating the release of cytokines. This plays a critical role in the formation of atherosclerotic plaques and vascular wall remodeling (13,56).

Blocking autophagic flux. When autophagic flux is impaired, vascular cells (such as endothelial cells, macrophages and smooth muscle cells) are unable to effectively clear accumulated harmful substances (such as oxidized low-density lipoprotein and lipid droplets), leading to enhanced inflammation, lipid deposition and plaque formation. This further accelerates the progression of atherosclerosis (65).

Coronary artery disease

Amplifying inflammatory response. cPLA2 can amplify the inflammatory response within plaques by promoting the production of inflammatory mediators, leading to plaque instability and rupture. Following plaque rupture, thrombosis can be triggered, resulting in acute coronary syndromes (such as myocardial infarction) (65).

Prothrombotic effect. AA derivatives produced by cPLA2 (such as thromboxane A2) have a strong prothrombotic effect, promoting platelet aggregation and thrombosis formation. This creates favorable conditions for the onset of coronary heart disease (28).

Myocardial infarction

Exacerbating inflammatory response. After myocardial infarction, the activation of cPLA2 leads to the release of AA, which further synthesizes inflammatory mediators, such as prostaglandins and leukotrienes. These mediators promote the infiltration of inflammatory cells (such as macrophages and leukocytes), aggravating myocardial damage and necrosis, while delaying myocardial repair (65).

Promoting excessive myocardial cell apoptosis. During reperfusion therapy following acute myocardial infarction, excessive activation of cPLA2 may lead to excessive apoptosis of myocardial cells, exacerbating reperfusion injury (that is, reperfusion damage), which causes further myocardial cell death and functional loss (40).

Blocking autophagic flux. cPLA2 inhibits autophagic activity, preventing myocardial cells from effectively clearing damaged organelles. This leads to increased cell death, further exacerbating the damage caused by myocardial infarction (61,62).

Heart failure

Promoting inflammatory response and cell apoptosis. In heart failure, cPLA2 promotes myocardial cell apoptosis and fibrosis by activating downstream inflammatory and fibrosis pathways, leading to the deterioration of cardiac structure and function. cPLA2 may regulate the activity of fibroblasts, promoting collagen deposition and increasing the stiffness of the heart, thereby worsening heart failure (37-39).

Hypertension

Endothelial injury. Increased activity of cPLA2 leads to the breakdown of phospholipids in endothelial cell membranes, which in turn affects the vasomotor function of blood vessels (76). Endothelial damage is a key feature of hypertension and by altering endothelial cell function, cPLA2 may exacerbate endothelial permeability and vascular stiffness (13), further worsening hypertension.

Regulation of the renin-angiotensin system. Studies suggest that cPLA2 may be involved in regulating the action of angiotensin II (Ang II), a significant trigger of hypertension (3,78). By affecting this system, cPLA2 may indirectly contribute to the elevation of blood pressure.

Valvular heart disease

Triggering inflammatory response and oxidative stress. In valvular heart diseases (such as rheumatic heart disease and degenerative valve disease), chronic inflammation over time leads to the destruction and proliferation of valve tissue (79) and the activation of cPLA2 exacerbates this process. Increased activity of cPLA2 may intensify the generation of free radicals, thereby aggravating the pathological damage in valve disease (1).

Affecting the function of valve cells. Activation of cPLA2 alters the function of valve cells (such as fibroblasts and smooth muscle cells), promoting the proliferation, migration and collagen synthesis of these cells (37-39). This may lead to pathological changes such as thickening, calcification and fibrosis of the valve, thus worsening the progression of valvular heart disease.

7. Conclusion and prospects

cPLA2 plays a critical role in the onset and progression of cardiovascular diseases, particularly in processes such as inflammatory response, platelet activation, myocardial cell apoptosis and autophagy. By catalyzing the hydrolysis of phospholipids to release arachidonic acid, cPLA2 triggers a cascade of biological reactions that promote inflammation and thrombosis, thereby exacerbating the progression of atherosclerosis, myocardial infarction, heart failure and other cardiovascular diseases. Additionally, cPLA2 holds significant potential as a biomarker, with its activity guiding early diagnosis (25), risk assessment and prognosis evaluation in cardiovascular diseases (80,81). Several studies have shown that inhibiting cPLA2 activity (for example by using inhibitors such as AACOCF3) can effectively alleviate inflammation, thrombosis, myocardial damage and other issues associated with cardiovascular diseases (82-84). However, its clinical application faces challenges, including lack of specificity, unstandardized detection methods, limited large-scale validation and the influence of various external factors. Moreover, the development of cPLA2 inhibitors shows promise for clinical treatment, but challenges remain in terms of selectivity, pharmacokinetics and safety. Preclinical and clinical trial results (for example LY3159200, developed by Eli Lilly and Company) have demonstrated promising efficacy in experimental settings, but further exploration is needed regarding their safety, long-term effects and side effects (85).

In conclusion, cPLA2 inhibitors represent a novel therapeutic approach for cardiovascular diseases. Their future development depends on more precise drug design, comprehensive clinical validation and thorough evaluation of long-term efficacy. By

addressing existing technological and clinical challenges, cPLA2-targeted therapies have the potential to offer new treatment options for cardiovascular disease patients, improve quality of life and reduce the incidence of cardiovascular events.

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Availability of data and materials

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Authors' contributions

GS was involved in the conception of the study, and the formulation and evolution of overarching study goals and aims. XC was responsible for project administration and article revision. WL was involved in manuscript preparation, presentation of the information and figures, and writing the initial draft (including substantive translation). SW contributed by preparing the manuscript, specifically its critical review, commentary and revision at pre-publication stages. RL performed study revisions and improvements. DZ and XQ drew the table and diagrams and performed revisions. JZ, ZL and MM were involved in the analysis of the information. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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