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# Does Doxorubicin Cause Heart Damage by Interfering With Heart Energy Metabolism?*

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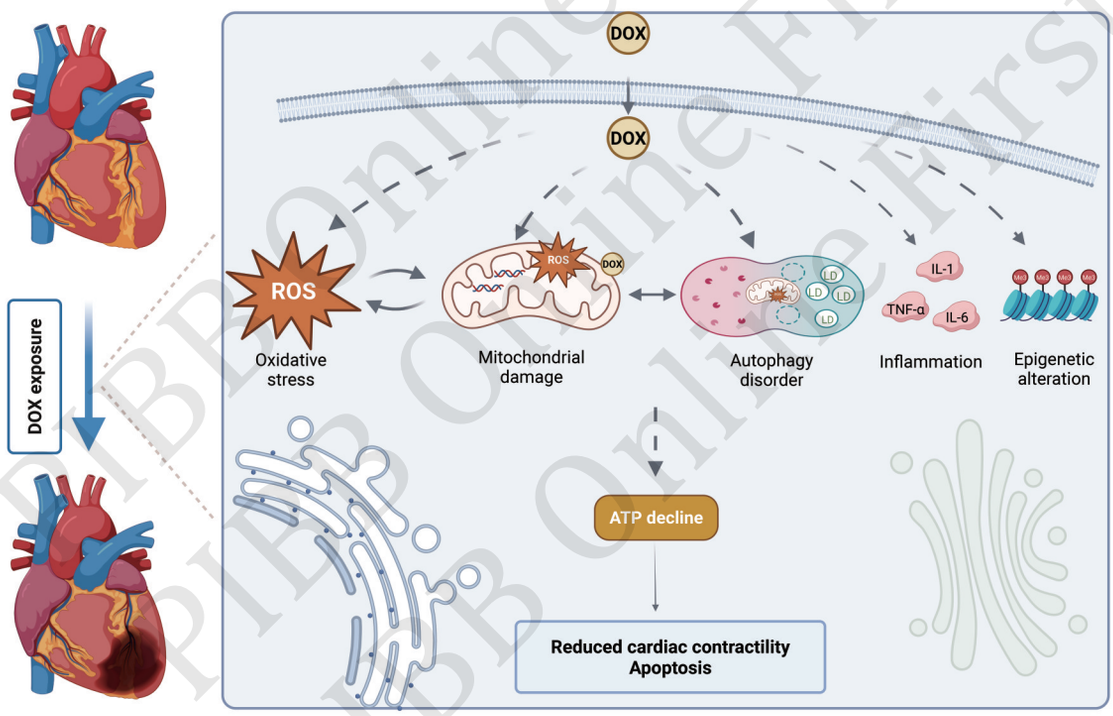
## Graphical abstract






**Abstract** As oncologic therapies continue to advance, the overall survival of cancer patients has markedly increased. Nevertheless, virtually every anticancer treatment modality is accompanied by some degree of cardiotoxicity. Epidemiological data

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indicate that approximately 30 % of cancer survivors ultimately die from cardiovascular disease. Among the cardiotoxic agents, the anthracycline doxorubicin (DOX) is the most widely used; it effectively suppresses a variety of malignant tumors—including breast cancer, lymphoma, and acute leukemia—but its cardiac toxicity limits further escalation of clinical dosing. Literature reports identify a cumulative dose of ≥250 mg/m² as the threshold of high risk, with roughly 25 % of patients receiving DOX developing varying degrees of myocardial injury; severe cases progress to heart failure. Even at cumulative doses below the traditional safety limit, some patients exhibit cardiac dysfunction after the first administration, suggesting that cardiotoxicity is not solely a linear function of dose. DOX related cardiotoxicity can be classified as acute (hours to days after administration), sub acute (weeks to months), and chronic/late onset (years later). Most patients initially exhibit only mild reductions in left ventricular ejection fraction (LVEF) or subtle abnormalities in global longitudinal strain (GLS), often without symptoms. Recently, cardiac biomarkers (cTn, NT proBNP) combined with high sensitivity echocardiography (speckle tracking) have been recommended for monitoring high risk individuals, enabling detection of subclinical injury before overt LVEF decline. Currently, several preventive and therapeutic approaches are used in clinical practice, which can be summarized into the following four points: (1) dose limitation and administration strategies: fractionated low dose regimens, liposomal encapsulation, or continuous infusion lower peak plasma concentrations, thereby reducing cardiac exposure; (2) pharmacologic prophylaxis: β blockers (*e.g.*, carvedilol) and ACE inhibitors/ARBs have shown protective effects on LVEF in some randomized trials, though results remain inconsistent and require larger confirmatory studies; (3) metabolic targeted interventions: animal experiments indicate that activation of PPARα or supplementation with L carnitine restores fatty acid oxidation and improves ATP generation, suggesting metabolic modulators as promising cardioprotective candidates; (4) lifestyle modifications: regular aerobic exercise up regulates mitochondrial biogenesis genes (PGC-1α) and reduces reactive oxygen species (ROS) production; small clinical studies have demonstrated a potential benefit in attenuating cTnT elevation. However, DOX-induced cardiotoxicity has not been effectively controlled, indicating that the core mechanism underlying DOX-related cardiac toxicity remains unidentified. Cardiomyocytes are high energy demand cells, and metabolic dysregulation is considered a central component of DOX induced cardiotoxicity. DOX disrupts myocardial metabolic balance through several interrelated pathways. (1) Oxidative stress and mitochondrial damage: DOX generates abundant ROS within cells, leading to mitochondrial membrane potential loss, lipid peroxidation, and iron accumulation, which suppress electron transport chain activity and markedly reduce ATP synthesis efficiency. (2) Autophagy dysregulation: DOX interferes with autophagic flux, preventing the clearance of damaged mitochondria and further aggravating apoptosis and inflammatory responses. (3) Inflammation and cytokine release: oxidative stress activates NF- κB, up-regulating pro inflammatory cytokines such as TNF- α and IL-6, creating a chronic inflammatory microenvironment that weakens myocardial contractility. (4) Epigenetic modifications: studies have shown that DOX alters DNA methylation and histone acetylation patterns in cardiomyocytes, affecting the expression of key metabolic genes (*e.g.*, PGC-1α, CPT-1) and further inhibiting fatty acid β oxidation. These mechanisms collectively lead to suppressed fatty acid oxidation and compensatory up regulation of glycolysis, manifested by an elevated lactate/pyruvate ratio, accumulation of medium chain acyl carnitines, and a pronounced decline in ATP production. The resulting energy deficit precipitates left ventricular contractile dysfunction and, ultimately, heart failure. Despite extensive basic and clinical research on DOX cardiotoxicity, a unified risk assessment model and precise interventions targeting metabolic disturbances remain lacking. This review systematically summarizes recent progress on DOX induced cardiotoxicity and highlights that impairment of myocardial energy metabolism is a central mechanism of injury, thereby deepened our understanding of how impaired myocardial energy metabolism drives DOX induced injury, we can move toward safer chemotherapy protocols that achieve "cure cancer without harming the heart".

**Key words** doxorubicin, cardiotoxicity, myocardial injury, energy metabolism

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Cardiovascular disease and cancer remain the top two contributors to global mortality. Contemporary multidisciplinary advances in tumor diagnosis and therapy have markedly prolonged cancer-patient survival. However, the onset and fatality of cardiotoxicity linked to anti-cancer therapies continue to rise. Reports indicate that approximately 30% of long-term cancer survivors now ultimately succumb to cardiovascular disease rather than to the original malignancy[1]. Doxorubicin (DOX) is one of the most effective broad-spectrum anticancer anthracycline drugs in clinical use. It is effective in treating solid malignant tumors (bladder, breast cancer, lung cancer, *etc*.) and hematological tumors (Hodgkin's disease,

non-Hodgkin's lymphoma and pediatric leukemia, *etc*.)[2]. Nevertheless, DOX carries a well-recognized and dose-dependent cardiotoxic liability that may present across the entire clinical spectrum—from transient arrhythmias and acute hypertensive spikes to lymphocytic myocarditis, overt congestive heart failure, and ultimately fatal cardiogenic shock[3]. Clinical evidence summarized in Table 1 a clear dose-response relationship for DOX-related cardiotoxicity: the cumulative incidence of heart failure rises from 3% at 400 mg/m² to 7% at 550 mg/m² and reaches 18% once the exposure attains 700 mg/m²[4]. Elucidating the molecular mechanisms that drive this dose-dependent cardiac injury is therefore an urgent research priority.

**Table 1 Relationship between cumulative dose of DOX and heart failure** [4]

| Cumulative dose/（mg·m$^{-2}$） | Incidence of heart failure/% |
|---|---|
| 400 | 3–5 |
| 550 | 7–26 |
| 700 | 18–48 |

The heart is a high-output metabolic organ that cycles approximately 30 kg of adenosine triphosphate (ATP) per day—equivalent to 20–30 times its own dry weight[5]. It primarily utilizes fatty acids, glucose, amino acids, and other substrates to generate ATP via oxidative phosphorylation[6-7]. Recent researches suggest that the pathogenesis of DOX-induced cardiotoxicity, which compromises cardiac function, is linked to oxidative stress, mitochondrial damage, inhibition of autophagy, pro-inflammatory responses, and other mechanisms, potentially culminating in cardiomyocyte apoptosis. Currently, therapeutic strategies predominantly involve targeted pharmacological interventions, such as dexrazoxane (DXZ), the sole protective agent approved by the American Food and Drug Administration (FDA)and European Medicines Agency (EMA) for DOX-induced cardiotoxicity (DIC). DXZ functions by inhibiting reactive oxygen species (ROS) and preventing DNA double-strand breaks. It is administered intravenously 30 min prior to DOX treatment at a dosage ten times that of DOX. However, DXZ may exacerbate bone marrow suppression and potentially diminish the efficacy of chemotherapy; thus, its use is primarily recommended for high-risk patients[8]. Protosappanin A (PrA), an active constituent of Caesalpinia sappan, has demonstrated abilities to inhibit lipid peroxidation and the release of free $Fe^{2+}$. In murine models, a dosage of 20 mg/kg PrA has been shown to reverse the decrease in ejection fraction (EF) induced by DOX[9]. Furthermore, the stabilization of mitochondrial membrane potential by the mitochondrial-targeting agent MitoQ has been observed to mitigate the damage inflicted by DOX treatment in H9C2 cells[10]. Our previous study has demonstrated that erianin protects against doxorubicin-induced myocardial injury *via* Keap1-Nrf2 signaling pathway activation. Despite these interventions, their efficacy remains limited, and the primary underlying mechanism has yet to be identified. We propose that energy metabolism disorder constitutes the central mechanism of DOX-induced myocardial injury. This review consolidates current evidence to clarify how DOX provokes oxidative stress, mitochondrial injury, autophagy, inflammation, epigenetic modifications, and their synergistic interplay ultimately disturbs energy homeostasis. By elucidating the central mechanism of DOX-induced myocardial injury, this research seeks to provide a theoretical foundation for addressing the cardiac side effects associated with DOX chemotherapy.

## 1 DOX disrupts cardiomyocyte energy homeostasis by triggering oxidative

Oxidative stress is a condition characterized by an imbalance between the body's antioxidant defense system and the excessive production of ROS and reactive nitrogen species (RNS). This imbalance is considered one of the primary causes of DIC[11]. Elevated levels of oxidative stress and a subsequent decline in antioxidant status have been observed in cancer patients undergoing DOX treatment.

On one hand, the polycyclic quinone nucleus of anthracyclines coordinates $Fe^{2+}$/$Fe^{3+}$ through the C11-C12 carbonyl oxygens, generating an octahedral chelate. This complex is inhibited by the NADH dehydrogenase complex (complex I) located within the inner mitochondrial membrane. The enzyme's flavin mononucleotide (FMN) cofactor donates the first electron to the anthracycline quinone, reducing it to a labile semiquinone radical, while $Fe^{3+}$ is concurrently reduced to $Fe^{2+}$. The semiquinone rapidly transfers a second electron to molecular

oxygen, resulting in the formation of superoxide anion ($O_2\cdot^-$), while $Fe^{2+}$ facilitates the Fenton reaction to produce hydroxyl radical ( · OH). The disproportionation of $O_2\cdot^-$, catalyzed by superoxide dismutase, further generates $H_2O_2$. Consequently, an anthracycline-Fe redox cycle is established, which continuously amplifies the formation of reactive oxygen species[12-14].

On the other hand, DOX activates several oxidative stress-related signaling pathways, notably the Nrf2/Keap1/ARE signaling pathway[15]. Under physiological conditions, Nrf2 binds to Keap1 to form a complex. Upon cellular stimulation, Nrf2 dissociates from the Nrf2-Keap1 complex and translocates to the nucleus, where it interacts with the antioxidant response element (ARE) to enhance the expression of antioxidant enzymes[16-17]. Treatment with DOX has been shown to significantly elevate Keap1 levels while suppressing Nrf2 expression, thereby exacerbating oxidative stress (the specific regulatory mechanism is detailed in Table 2)[18]. Additionally, the Sirt1/p66Shc signaling pathway is involved[19]. During oxidative stress, p66Shc can associate with cytochrome C released from mitochondria, leading to the oxidation of cytochrome C and subsequently enhancing ROS production[20]. DOX elicits a selective up-regulation of miR-34a-5p, which silences Sirt1 deacetylase and consequently disinhibits p66Shc, culminating in amplified mitochondrial oxidative stress[21-22]. The Sirt1/PPAR/PGC-1α signaling pathway involves in regulating energy metabolism, cell proliferation, cell differentiation, development, and apoptosis in cardiomyocytes[23]. A research indicates that DOX can downregulate PPAR expression by modulating Sirt1, thereby activating oxidative stress and inflammation, and leading to mitochondrial dysfunction[24]. PPAR coactivator 1α (PGC-1α) is an inducible transcription coactivator of PPAR that enhances its nuclear transcriptional activity and is vital for mitochondrial regulation[25]. DOX is known to impair antioxidant capacity and induce oxidative stress by decreasing Sirt1 expression and PGC-1α level[26-27]. Furthermore, the cationic anthracycline irreversibly docks to the anionic head groups of cardiolipin, driving its electrostatic sequestration within the inner mitochondrial membrane and precipitating uncontrolled ROS generation[28-30].

**Table 2 Mechanism of DOX−induced changes in corresponding genes or proteins**

| Gene/protein | Variation | Mechanism |
|---|---|---|
| Keap1 | Increase | DOX disrupts ubiquitination/deubiquitination recruitment proteins and autophagy inhibits Keap1 degradation [18] |
| *miR-34a-5p* | Increase | DOX activates NF-κB and p53 signaling to activate miR-34a-5p transcription [22] |
| *Sirt1* | Reduction | DOX increased the expression of miR-34a-5p and inhibited Sirt1 [22] |
| TRPC3/6 | Increase | DOX activates NFAT signaling pathway [31] |
| Mtfp1 | Increase | It was used as a mitochondrial division marker without studying its mechanism [32] |
| HDAC | Increase | DOX increased HDAC activity by increasing the expression of Rac1 [33] |
| DRP1 | Reinforcement | DOX activates PKA and enhances the phosphorylation of DRP1 [34] |
| OPA1 | Increase | It was used as a marker of mitochondrial fusion without studying its mechanism [35] |
| Nrf2 | Inhibition | DOX increases the expression of Keap1 and binds to Nrf2 to inhibit its activation [18] |
| *PGC-1α* | Reduction | DOX reduced the expression of Sirt1 and decrease the trancription of PGC-1α [27] |
| *ABCB8* | Reduction | DOX directly leads to the decrease of ABCB8 mRNA and protein levels [36] |
| MFN1/2 | Reduction | It was used as a marker of mitochondrial fusion without studying its mechanism [37] |
| DNMT1 | Inhibition | DOX inhibits the catalytic activity of DNMT1 *via* DNA intercalation [38] |
| MitoFer | Inhibition | It was used as a marker of mitochondrial iron transport without studying its mechanism [39] |
| NF-κB | Activation | DOX causes ROS production and activates NF-κB [40] |
| TNF-α/IL-1β/IL-6 | Increase | DOX activates NF-κB and leads to an increase in inflammatory factors [41] |

续表

| Gene/protein | Variation | Mechanism |
|---|---|---|
| Parkin/PINK1 | Decreases/Increases | It was used as a marker to regulate autophagy without studying its mechanism [42] |

Keep1: Kelch-like ECH-associated protein 1; miR-34a-5p: microRNA-34a-5p; Sirt1: Sirtuin 1; TRPC3/6: transient receptor potential canonical 3/6; Mtfp1: mitochondrial fission process 1; HDAC: histone deacetylase; DRP1: dynamin-related protein 1; OPA1: optic atrophy 1; Nrf2: nuclear factor erythroid 2-related factor 2; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ABCD8: ATP-binding cassette subfamily D member 8; MFN1/2: mitofusin 1/2; DNMT1: DNA (cytosine-5)-methyltransferase 1; MitoFer: mitochondrial ferritin; NF-κB: nuclear factor κB; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: Iinterleukin-6; Parkin: Parkin RBR E3 ubiquitin protein ligase; PINK1: PTEN-induced kinase 1.

The accumulation of ROS induced by the aforementioned mechanism adversely impacts the mitochondrial electron transport chain, specifically targeting complexes I, III, and IV. This results in diminished electron transport efficiency and increased electron leakage, which further exacerbates ROS production, thereby creating a self-perpetuating cycle that ultimately reduces ATP synthesis[43-45]. Additionally, ROS can induce lipid peroxidation of the mitochondrial membrane, compromising its structural integrity and function. This leads to increased membrane permeability, resulting in the leakage of mitochondrial matrix components and subsequently impairing mitochondrial energy production[46-47]. Furthermore, ROS directly damage mitochondrial DNA (mtDNA), disrupting the transcription and translation of mitochondrial genes. This disruption affects the synthesis of proteins related to mitochondrial function, thereby impairing normal mitochondrial function and energy metabolism[48-49].

Oxidative stress induced by DOX also reduces the activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase in cells, resulting in a decrease in the ability of cells to scavenge ROS, resulting in excessive accumulation of ROS in cells, thereby interfering with the normal metabolic process of cells[50-52]. In addition, DOX can be combined with glutathione to form a mixed disulfide, which reduces the level of glutathione, resulting in a decrease in cell antioxidant capacity and an increase in ROS, thereby affecting energy metabolism[53].

Oxidative stress also leads to changes in energy metabolism-related enzyme activity, such as glycolysis-related enzymes[54], tricarboxylic acid cycle-related enzymes, and ATP synthase[55-56], resulting in abnormal energy metabolism. Finally, oxidative stress can cause changes in energy metabolism-related signaling pathways. For example, oxidative stress can increase intracellular AMP levels and activate AMPK signaling pathways[57]. However, excessive activation of the AMPK signaling pathway inhibits processes such as fatty acid synthesis and protein synthesis, thereby affecting cell energy metabolism[58-59]. And mTOR signaling pathway, which plays a key role in cell growth, proliferation and metabolic regulation, while ROS can inhibit mTOR signaling pathway, thus affecting cell protein synthesis, autophagy and mitochondrial biosynthesis, thereby affecting cell energy metabolism[60-61].

In conclusion, DOX induces substantial ROS production, primarily due to its glycoside ligands, their iron complexes, and subsequent binding to mitochondrial cardiolipin, thereby initiating oxidative stress. The generated ROS adversely affect the mitochondrial electron transport chain, diminishing electron transport efficiency and subsequently decreasing ATP synthesis. Concurrently, ROS compromise the integrity of the mitochondrial membrane, damage mitochondrial DNA, and disrupt normal energy metabolism. Additionally, ROS reduce intracellular antioxidant enzyme activity, further interfering with standard metabolic processes. Ultimately, oxidative stress modifies the activity of enzymes and signaling pathways related to energy metabolism, thereby impacting cellular energy homeostasis and function. In summary, during cancer treatment, DOX generates significant ROS, leading to oxidative stress that damages mitochondria, impairs cellular antioxidant defenses, and alters metabolic enzyme activities and signaling pathways, culminating in metabolic dysfunction within cardiomyocytes.

## 2 DOX leads to myocardial energy metabolism disorder by destroying energy factory−mitochondria

Mitochondria, as organelles integral to metabolism, play a crucial role in energy production. The heart exhibits the highest mitochondrial content among all organs, with mitochondria occupying approximately 30% of the myocardial cell volume and contributing to over 90% of the energy requirements of the myocardium[62]. DOX not only induces mitochondrial damage through the mediation of oxidative stress but also leads to iron overload, disruptions in calcium homeostasis, alterations in mitochondrial dynamics and autophagy, as well as mutations, defects, and leakage of mtDNA, ultimately impairing mitochondrial ATP production.

### 2.1 Effect of DOX on mitochondrial ion concentration

The balance of ion concentration within mitochondria is crucial for energy production. Studies have shown that the hearts of patients with DIC exhibit excessive iron accumulation in mitochondria compared to both non-DIC patients and healthy individuals[36]. The mechanism is: DOX-induced mitochondrial ATP-binding cassette subfamily B member 8 (ABCB8) protein[36] and mitochondrial ferritin (MitoFer)[39] levels decreased, ABCB8 protein is mainly to control mitochondrial iron output. MitoFer protein can store free iron. It has also been reported that gene inactivation of MitoFer in rodents leads to an increase in DIC[39].

Research has demonstrated that DOX enhances the expression of TRPC3 and TRPC6 in adult rat ventricular myocytes, altering the transient characteristics of $Ca^{2+}$ dynamics[63]. Concurrently, DOX interacts with and modifies the activity of RyR2 and SERCA2A, thereby disrupting intracellular $Ca^{2+}$ homeostasis[64]. Additionally, DOX activates calmodulin-dependent protein kinase II (CaMKII), leading to sarcoplasmic reticulum $Ca^{2+}$ leakage[65]. These findings indicate that DOX induces calcium overload in cardiomyocytes, which subsequently diminishes mitochondrial calcium storage capacity and results in mitochondrial dysfunction[66-67].

### 2.2 Effect of DOX on mitochondrial dynamics

Mitochondrial dynamics encompass the processes of mitochondrial fission and fusion[68]. Excessive mitochondrial fission can trigger apoptosis, whereas mitochondrial fusion has the potential to inhibit this process[69-70]. Research has demonstrated that treatment with DOX results in an up-regulation of mitochondrial fission protein 1 (Mtfp1), a GTPase involved in mitochondrial fission, within cardiomyocytes[32]. Additionally, there is an observed increase in the phosphorylation of dynamin-related protein 1 (DRP1), a GTPase responsible for the rupture of the mitochondrial outer membrane[34, 71-72]. In contrast, the expression of mitomycin 1/2 (MFN1/2, mitochondrial fusion-related GTPase) was down-regulated[37], and the expression of optic atrophy protein 1 (OPA1, GTPase involved in mitochondrial fusion) was down-regulated[35]. The induction of mitochondrial fission by DOX leads to the collapse of the mitochondrial network and the accumulation of fragmented mitochondria, which in turn results in excessive ROS production. This cascade ultimately impairs ATP synthesis and precipitates a cellular energy crisis[73]. The excessive mitochondrial fission induced by DOX serves as a catalyst for the initiation of apoptosis.

### 2.3 Effect of DOX on mitochondrial DNA

DOX has been shown to induce alterations in mtDNA. The limited repair capacity of mtDNA—due to the absence of histones and its close proximity to ROS-producing sites—renders it highly susceptible to various forms of damage, including point mutations, deletions and reduced copy number[74]. These lesions lead to decreased activities of mtDNA-encoded respiratory chain enzymes such as NADH dehydrogenase (complex I) and cytochrome c oxidase (complex IV) [75], ultimately resulting in disrupted energy metabolism. Furthermore, recent studies have demonstrated that mtDNA can be released into the cytoplasm *via* BAX, BAK, and VDAC channels in induced pluripotent stem cell-derived cardiomyocytes obtained from the hearts of patients treated with DOX. This release activates the cGAS-STING pathway, leading to inflammation and further contributing to abnormal energy metabolism[76].

### 2.4 DOX regulation of mitophagy

Mitochondrial autophagy, or mitophagy, is a crucial physiological process responsible for the removal of damaged mitochondria, thereby preventing the accumulation of cellular damage[73], During this process, compromised mitochondrial membranes and

internal macromolecules are degraded into amino acids, glucose, and nucleotides, which are subsequently utilized in cellular biosynthesis and energy metabolism[77]. Mitophagy can be categorized into two distinct types: receptor-dependent and receptor-independent. The receptor-dependent pathway is predominantly facilitated by specific proteins located on the mitochondrial surface[78], whereas the receptor-independent pathway is primarily mediated by the Parkin family of proteins. This latter pathway involves the ubiquitination of mitochondrial proteins and the subsequent fusion of mitochondria with lysosomes[79]. Empirical studies have demonstrated a bidirectional pattern of autophagy in the cardiac tissue of mice treated with DOX. Within one week of treatment, there was a marked reduction in the expression levels of Parkin and PINK1, leading to the accumulation of mitochondrial damage. By the 14th day post-treatment, the expression of Parkin and PINK1 increased significantly, resulting in an uncontrolled cascade of enhanced autophagy and the depletion of the mitochondrial population[42, 80]. Mitochondrial damage accumulation and quantity consumption will lead to blocked ATP production.

In summary, DOX induces mitochondrial damage or dysfunction through 5 primary pathways: it induces oxidative stress, impairs mitochondrial function; it disrupts mitochondrial dynamics by promoting fission, inhibiting fusion, and causing the collapse of the mitochondrial network along with energy metabolism disorders; it interferes with mitophagy, in either the accumulation or depletion of mitochondria; it leads to iron overload and calcium imbalance, contributes to mitochondrial damage; and it compromises the mitochondrial DNA repair system, causing leakage that activates the cGAS-STING inflammatory pathway, affects myocardial energy metabolism. Given that mitochondria are the principal organelles responsible for ATP production in cardiomyocytes, the central mechanism underlying DOX-induced myocardial injury is its detrimental impact on the energy metabolism of these cells.

## 3 DOX causes abnormal energy metabolism of cardiomyocytes by damaging autophagy homeostasis

Recent studies have indicated that the autophagic processes in pressure-overloaded cardiomyocytes become dysregulated, ultimately resulting in cardiac dysfunction and heart failure[81-82]. Autophagy in cardiomyocytes is crucial for regulating energy metabolism. It serves a dual function: firstly, it facilitates the selective removal of damaged mitochondria *via* mitophagy, thereby preserving cellular homeostasis; secondly, it supplies energy substrates to cardiomyocytes through the autophagic degradation of lipid droplets[83]. Lipophagy involves the lysosomal degradation of lipid droplets, wherein triglycerides are hydrolyzed into fatty acids by acidic hydrolases and subsequently oxidized through mitochondrial β -oxidation to fulfill the energy requirements of cardiomyocytes[84]. Given that the heart is an organ with a high dependency on fatty acid metabolism for its energy supply, and considering that fatty acids are predominantly stored in lipid droplets, any impairment in autophagy can significantly disrupt cardiac fatty acid metabolism.

In the aforementioned discussion on "mitochondrial damage", it is indicated that DOX treatment initially results in the inhibition of autophagy. This inhibition, combined with the degradation of lipid droplet autophagy, leads to a reduction in energy substrates and a consequent shortage of energy supply. Subsequently, autophagy is reactivated, triggering excessive lipid phagocytosis and an accumulation of free fatty acids. The surplus of free fatty acids induces myocardial lipid toxicity, thereby impairing cardiac function[85-87]. Concurrently, the overload of free fatty acids can disrupt mitochondrial metabolism, leading to the production of excessive reactive oxygen species and causing further damage.

In conclusion, DOX initially induces autophagy inhibition during the early stages of treatment, which is subsequently followed by autophagy activation. The initial inhibition of autophagy results in the accumulation of damaged mitochondria and impaired degradation of lipid droplets, ultimately leading to an inadequate energy supply. Conversely, the activation of autophagy results in mitochondrial depletion and excessive degradation of lipid droplets, causing disruptions in energy metabolism and lipid toxicity. Overall, the administration of DOX in cancer treatment is associated with autophagic dysregulation, contributing to aberrant metabolic processes in myocardial cells.

## 4 DOX causes energy metabolism disorders by causing inflammation

Inflammation is a critical factor in the pathogenesis of DOX-induced cardiomyopathy. Empirical evidence indicates that DOX administration significantly elevates inflammatory mediators by activating nuclear factor κB (NF-κB), including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [40-41]. These inflammatory mediators precipitate substantial disruptions in energy metabolism. Specifically, pro-inflammatory cytokines such as TNF- α, IL-1, and IL-6 up-regulate leptin expression, which subsequently suppresses appetite and enhances energy expenditure[88]. Additionally, leptin stimulates the secretion of glucagon-like peptide-1 (GLP-1) in the intestine, which augments insulin secretion, increases energy expenditure, and reduces food intake[89-90]. Furthermore, IL-6 plays a pivotal role in inducing insulin resistance, thereby impairing cellular glucose uptake and utilization, elevating blood glucose levels, and disrupting energy metabolism[91]. Finally, a large amount of ROS is produced during the inflammatory process, causing oxidative stress and affecting energy metabolism[92]. All in all, DOX in the treatment of cancer, will cause inflammation, resulting in abnormal metabolism of myocardial cells.

## 5 DOX affects energy metabolism through epigenetic modification

DNA methylation is an important process of regulating gene transcription[93]. Studies have shown that DOX exposure reduces cardiac DNA methyltransferase-1 (DNMT1) activity in rats[38], leading to promoter hypomethylation and consequent functional impairment of PGC-1α, nuclear respiratory factor-1 (NRF-1), and mitochondrial transcription factor A (TFAM)[94].

Histone modifications play a crucial role in regulating gene expression by altering chromatin structure. Research indicates that the histone deacetylase (HDAC) family is significantly up-regulated in the hearts of rats treated with DOX, leading to histone deacetylation. This process results in a more condensed chromatin structure and the subsequent inhibition of metabolism-related gene transcription[33]. For instance, the HEY2-HDAC1 axis is essential for maintaining cellular energy metabolism balance by regulating the transcription of mitochondrial energy metabolism genes. When HDAC1 undergoes deacetylation, chromatin becomes less accessible, thereby inhibiting the transcription of these genes and reducing mitochondrial energy production[95]. Furthermore, DOX treatment has been shown to gulate histone lysine demethylase (KDM3A) while down-regulating lysine-specific demethylase 1 (LSD1) in H9C2 cardiomyocytes, leading to aberrant histone methylation. Histone methylation can either activate or repress gene transcription, thus influencing energy metabolism[96].

Epigenetic modifications possess the capacity to alter gene function and are associated with various diseases as well as natural developmental processes. Research indicates that treatment with DOX can induce DNA methylation and histone modifications, leading to disruptions in energy metabolism. Consequently, the administration of DOX in cancer therapy is linked to aberrant DNA methylation and histone modifications, which subsequently result in impaired metabolic function in cardiomyocytes.

## 6 The synergistic interplay among the mechanisms

DOX-induced cardiotoxicity is not attributable to a singular pathway but rather to a complex interplay of oxidative stress, mitochondrial damage, autophagy imbalance, inflammatory responses, and epigenetic reprogramming. Once DOX penetrates the myocardium, an immediate burst of reactive oxygen species occurs. These ROS detrimentally affect the mitochondrial electron transport chain, leading to electron leakage and further exacerbating ROS generation[43-45]. On other side, the DOX inhibits the mitophagy at the early stage *via* disrupting the Parkin/PINK1 pathway, resulting in the accumulation of damaged mitochondria and persistent ROS leakage. When ATP levels fall below a critical threshold, autophagy becomes excessively activated, leading to the rapid degradation of mitochondria and lipid droplets by lysosomes. This process not only depletes the energy-producing organelles but also releases excessive free fatty acids, contributing to lipotoxicity and substrate imbalance[42, 80]. Additionally, ROS activate the NF-κB pathway, inducing the production of pro-inflammatory cytokines such as TNF-α and IL-

6, which in turn further stimulate ROS production[40-41]. Ultimately, DOX induces epigenetic changes that alter the activity of genes related to mitochondrial metabolism, leading to a prolonged suppression of the transcriptional program for energy metabolism[33, 94-95]. Although no study has simultaneously examined all of the aforementioned mechanisms, we posit that each is activated during DOX-based chemotherapy; their temporal sequence and relative magnitude remain to be defined. Whether operating singly or synergistically, these pathways converge on a final common phenotype—cellular energy-metabolic failure—that may constitute a novel therapeutic target for the prevention and treatment of DOX-related cardiotoxicity.

## 7 The end point of abnormal energy metabolism−cell death

It has been reported that myocardial cell death is the main cause of cardiovascular disease, including myocardial ischemia-reperfusion injury[97], Cardiomyopathy and cardiac fibrosis[98]. Most cardiomyocyte death is performed by programmed cell death, including apoptosis, pyroptosis, necrosis, and ferroptosis. These forms of programmed cell death are a major feature of the pathogenesis of various heart diseases[99]. The disorder of energy metabolism caused by DOX treatment can cause programmed cardiomyocyte death[100].

The apoptotic pathway is the most clearly characterized programmed cell death pathway, and it is also the most studied cell death pathway in DIC. First of all, DOX can lead to changes in mitochondrial membrane permeability, so that cytochrome c is released from mitochondria to the cytoplasm, combined with intracellular apoptotic protease activator-1 (Apaf-1) to form apoptotic bodies, activate caspase-9 and a series of caspase enzymes, leading to the destruction of cell structure and function, and ultimately leading to apoptosis[2, 101-102]. In addition, DOX leads to a decrease in ATP production, and many active processes of cell transport and various biochemical reactions that require energy are affected, resulting in intracellular ion balance being broken, thereby triggering apoptosis[103].

## 8 Conclusion and perspective

This article presents a systematic review of the various mechanisms through which DOX induces myocardial injury, primarily by affecting energy metabolism. The main mechanisms include oxidative stress, mitochondrial damage, dysregulation of autophagy, inflammatory responses, and epigenetic modifications, as illustrated in Figure 1. DOX is known to induce oxidative stress, leading to the generation of substantial amounts of ROS, which compromise mitochondrial structure and function, and damage mitochondrial DNA. Furthermore, DOX directly impacts mitochondrial dynamics, disrupts mitophagy, impairs the mitochondrial DNA repair system, induces membrane leakage, and causes iron overload and calcium imbalance. Concurrently, DOX treatment results in autophagy dysregulation, impairing the autophagic processes of mitochondria and lipid droplets. Additionally, it triggers an inflammatory response that further exacerbates oxidative stress. Finally, DOX induces DNA methylation and histone modifications, leading to alterations in genes associated with mitochondrial metabolism. In conclusion, these mechanisms collectively contribute to the adverse effects of DOX treatment, resulting in abnormal metabolism of myocardial cells, ion disorders, apoptosis, decreased myocardial contractility, and ultimately, cardiac dysfunction.

DOX-induced myocardial injury represents a complex, multi-faceted pathological process. Research involving cultured cells, intact rodents, and chemotherapy patients has identified distinct yet overlapping molecular cascades, with variations in their precise signatures and contributions depending on the biological context. Nonetheless, these model-specific pathways converge on 5 core mechanisms discussed herein: oxidative stress, mitochondrial damage, autophagic dysregulation, inflammatory signaling, and epigenetic reprogramming. Collectively, these mechanisms culminate in a common phenotype characterized by cardiac energy-metabolic failure.

Understanding the mechanisms of energy metabolism in DOX-induced myocardial injury is of paramount importance. This understanding facilitates the development of targeted cardioprotective strategies, which include regulating energy metabolism-related enzyme activities, enhancing antioxidant capacity, and maintaining mitochondrial function. These strategies mitigate the cardiotoxic

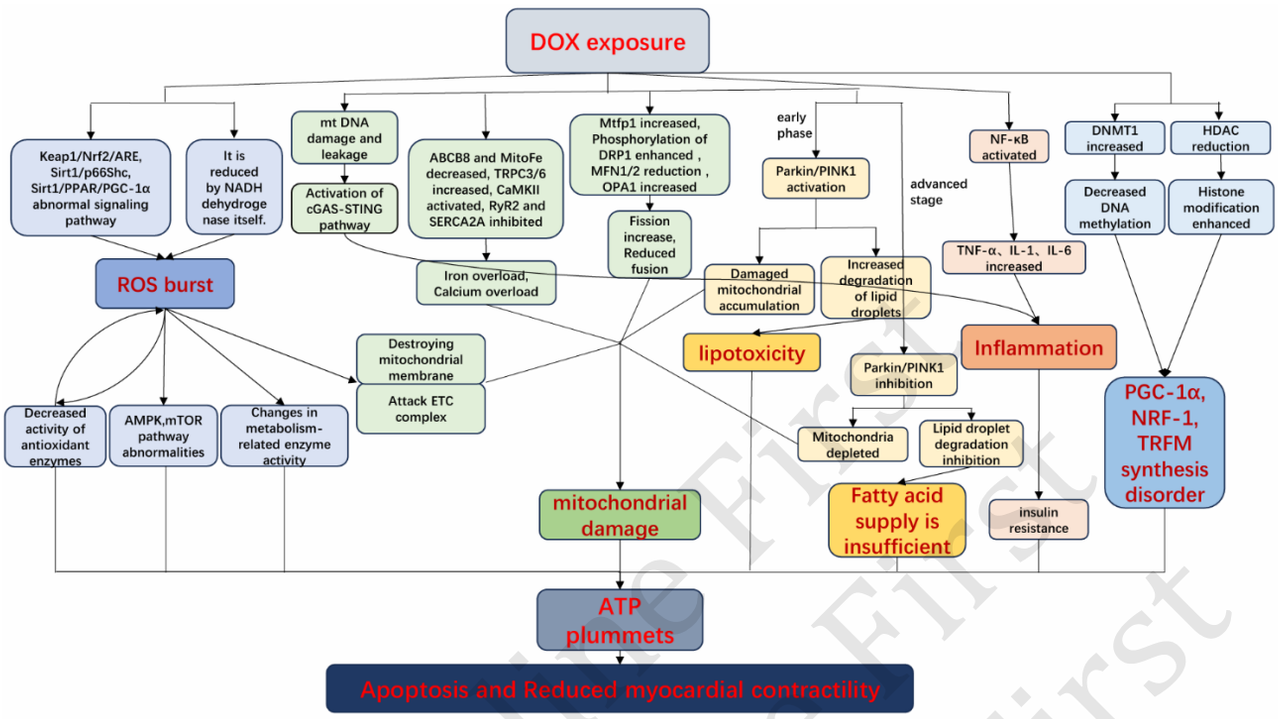


**Fig. 1　The general framework of the mechanism of abnormal myocardial energy metabolism induced by DOX**

It demonstrates the upstream incentives and downstream outcomes of DOX-induced oxidative stress, mitochondrial damage, autophagy disorders, inflammation, epigenetics, and ultimately ATP reductionTP leading to cardiomyocyte apoptosis and systolic dysfunction. DOX: doxorubicin; Keap1: Kelch-like ECH-associated protein 1; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; Sirt1: Sirtuin 1; p66Shc: 66-kDa Src homology 2 domain-containing protein; PPAR: peroxisome proliferator-activated receptor; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; AMPK: 5′ AMP-activated protein kinase; mTOR: mechanistic target of rapamycin; NADH: nicotinamide adenine dinucleotide (reduced form); mt DNA: mitochondrial DNA; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; ETC: electron transport chain; ABCB8: ATP-binding cassette sub-family D member 8; MitoFer: mitochondrial Ferritin; TRPC3/6: transient receptor potential canonical 3/6; CaMKII: calcium/calmodulin-dependent protein kinase II; RyR2: ryanodine receptor 2; SERCA2A: sarco/endoplasmic reticulum $Ca^{2+}$-ATPase 2a; Mtfp1: mitochondrial fission process 1; DRP1: dynamin-related protein 1; MFN1/2: mitofusin 1 / 2; OPA1: optic atrophy 1; Parkin: Parkin RBR E3 ubiquitin protein ligase; PINK1: PTEN-induced kinase 1; NF-κB: nuclear factor κB; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6; DNMT1: DNA (cytosine-5)-methyltransferase 1; HDAC: histone deacetylase; NRF-1: nuclear respiratory factor 1; ROS: reactive oxygen species; ATP: adenosine triphosphate.

effects of DOX and enhance the safety and efficacy of cancer treatments. Furthermore, it enables the identification of biomarkers and methodologies for the early detection and monitoring of cardiotoxicity, allowing for timely intervention in cardiac injury and improving patient prognosis. Ultimately, these insights contribute to the development of novel anticancer drugs that retain therapeutic efficacy while minimizing disruption to myocardial energy metabolism, thereby reducing the risk of cardiotoxicity.

Currently, numerous studies have investigated the mechanisms underlying myocardial injury induced by DOX. Nevertheless, identifying the pivotal pathway of DOX-induced myocardial toxicity remains crucial. Historically, numerous studies on DOX have primarily concentrated on mechanisms such as oxidative stress, mitochondrial damage, autophagy disorder, and inflammation. However, the majority of these investigations have been confined to the description of signaling pathways or morphological changes. Indicators that accurately reflect myocardial dysfunction remain largely restricted to traditional clinical parameters, including ejection fraction and troponin levels. Currently, predominant therapeutic approaches emphasize drug-targeted interventions, such as dexrazoxane, Protosappanin A, and the mitochondrial-targeting

agent MitoQ. Nonetheless, these existing treatments exhibit limited efficacy and have yet to identify a central mechanistic link. Given that myocardial cells are highly energy-dependent, we propose that disruptions in energy metabolism constitute the central mechanism of myocardial injury. This paper concentrates on the energy metabolism of myocardial cells, synthesizing existing research findings, and concludes that DOX-induced myocardial cell injury ultimately leads to energy metabolism disorders. It is posited that interventions aimed at restoring the energy supply to myocardial cells during DOX treatment may effectively mitigate its cardiotoxic effects. Our previous research identified that erianin can mitigate the production of reactive oxygen species and confer a protective effect against DOX-induced myocardial injury. Future research will focus on further elucidating its relationship with energy metabolism and exploring additional strategies to ameliorate energy metabolism disorders.

The key problem that has not yet been solved is what threshold ATP decline needs to reach to trigger irreversible damage. Are there any differences in this threshold among different species, different ages or different metabolic backgrounds? Is the decrease of ATP synchronized in different subregions of cardiomyocytes (subsarcolemmal and perinuclear mitochondria)? Can early energy reprogramming (such as glycolysis compensation) delay the progression of toxicity? When and how long should the existing protection strategies that can partially restore ATP be intervened?

ATP reduction may be the "trigger" to initiate a series of subsequent cascade reactions. Future research should start from the core of "energy" in order to truly achieve a win-win situation between anticancer efficacy and cardiac safety. Of course, we also need to study the differences in the susceptibility of different individuals to DOX cardiotoxicity, as well as the relationship between gene polymorphisms and energy metabolism, so as to provide a basis for personalized medicine.

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# 阿霉素是通过干扰心脏能量代谢导致心脏损伤的么？*

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**摘要**　随着肿瘤治疗水平的提高，患者的生存期延长，但大多数治疗手段都具有心脏毒性，因此约30%癌症幸存者最终死于心脏疾病。阿霉素（doxorubicin，DOX）是一类广泛用于治疗多种恶性肿瘤的蒽环类药物，其抗肿瘤效果较好，但在使用DOX治疗后有高达1/4的患者会表现出心脏损伤，从而限制了该药物的临床应用。研究表明，DOX可以通过干扰心肌细胞内环境稳态或直接造成心肌细胞损伤，从而导致心脏功能障碍。尽管DOX心肌毒性的机制已被广泛研究，但仍未能有效解决其临床困境，说明其核心环节尚待明确。鉴于心肌细胞为高耗能细胞，能量代谢障碍可能是其毒性作用的关键所在。而DOX会通过导致氧化应激、线粒体受损、自噬紊乱、炎症以及表观遗传引起底物利用异常，造成脂肪酸氧化受抑而糖酵解代偿性增强，乳酸/丙酮酸比值升高，中链酰基肉碱堆积，最终导致ATP合成显著减少，心肌功能障碍甚至死亡。本文系统梳理了DOX心脏毒性的研究进展，并发现其可通过影响心肌细胞能量代谢导致心肌损伤和功能障碍，为改善DOX诱导的心脏毒性的预防和治疗提供新的见解。

**关键词**　阿霉素，心脏毒性，心肌损伤，能量代谢

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