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Role of acetylation in doxorubicin-induced cardiotoxicity

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ABSTRACT

As a potent chemotherapeutic agent, doxorubicin (DOX) is widely used for the treatment of a variety of cancers However, its clinical utility is limited by dose-dependent cardiotoxicity, and pathogenesis has traditionally been attributed to the formation of reactive oxygen species (ROS). Accordingly, the prevention of DOX-induced cardiotoxicity is an indispensable goal to optimize therapeutic regimens and reduce morbidity. Acetylation is an emerging and important epigenetic modification regulated by histone deacetylases (HDACs) and histone acetyltransferases (HATs). Despite extensive studies of the molecular basis and biological functions of acetylation, the application of acetylation as a therapeutic target for cardiotoxicity is in the initial stage, and further studies are required to clarify the complex acetylation network and improve the clinical management of cardiotoxicity. In this review, we summarize the pivotal functions of HDACs and HATs in DOX-induced oxidative stress, the underlying mechanisms, the contributions of noncoding RNAs (ncRNAs) and exercise-mediated deacetylases to cardiotoxicity. Furthermore, we describe research progress related to several important SIRT activators and HDAC inhibitors with potential clinical value for chemotherapy and cardiotoxicity. Collectively, a comprehensive understanding of specific roles and recent developments of acetylation in doxorubicin-induced cardiotoxicity will provide a basis for improved treatment outcomes in cancer and cardiovascular diseases.

1. Introduction

Cancer remains the most common cause of death worldwide, and cancer and heart disease are the principal causes of morbidity and mortality in industrialized countries [1]. As the population ages and therapies increase longevity, the number of cancer cases will certainly rise [2]. Although chemotherapeutics have substantially improved survival rates in cancer, they can cause an extensive range of cardiovascular complications. In particular, cardiotoxicity is an important issue facing cardiologists and oncologists [3], and could be caused by many types of antineoplastic agents.

Doxorubicin (DOX), classified as an anthracycline, is among the most commonly prescribed clinical anticarcinogens and shows substantial efficacy in a broad spectrum of cancers, including lymphomas, leukemias, Ewing and Kaposi sarcomas, as well as several solid tumors. However, the clinical benefit of DOX is limited by the risk of severe cardiotoxicity. Acute cardiotoxicity often results in arrhythmias, transient cardiac dysfunction and electrocardiogram changes, it is generally reversible and may also be reflected as myocardial damage and eventually progress to chronic or delayed cardiotoxicity. While chronic cardiotoxicity often results in heart failure, decreased cardiac function and subclinical myocardial function decline, it is generally with progressive changes [4]. Furthermore, DOX activates proapoptotic p53, p38, and JNK, Bax translocation, caspase-dependent apoptotic signaling, and the Fas/FasL/NFAT axis, leading to cardiomyocyte apoptosis [5,6]. In addition to apoptosis, DOX induces pyroptosis and autophagy [7,8]. Furthermore, excessive ROS are produced by electron exchange between

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Abbreviations

AMPK	Adenosine 5′-monophosphate (AMP)-activated protein kinase
CAT	catalase
COXIV	cytochrome *c* oxidase IV
CTRP3	C1q/tumor necrosis factor-related protein-3
Drp1	Dynamin-related protein 1
ERK	extracellular regulated protein kinases
FasL	Fas ligand
FGF21	fibroblast growth factor 21
Foxo3a	Forkhead box O3
GCLM	glutamate-cysteine ligase modifier subunit
GHSR1a	growth hormone secretagogue receptor-1a
GPX	glutathione peroxidases
GSH	glutathione
GST	glutathione S-transferase
HSP25	heat shock proteins 25
HO-1	heme oxygenase 1
IDH2	isocitrate dehydrogenase 2
IGF2BP1	IGF2 mRNA binding protein 1
IL-1β	interleukin-1β
IL-6	interleukin-6
JAK/STAT	Janus kinase/signal transducer and activator of transcription
LKB1	liver kinase B1
MAPK	mitogen-activated protein kinase
mTOR	Mammalian Target of Rapamycin
MDA	malondialdehyde
MMP2	matrix metalloprotein-2
NFAT	nuclear factor of activated T-cell
NF-κB	nuclear factor kappa-B
NLRP3	NLR family pyrin domain containing 3
NQO1	NAD(P)H quinone oxidoreductase 1
NRF1	nuclear respiratory factor-1
Nrf2	nuclear erythroid factor 2-related factor 2
SOD	superoxide dismutase
OGG1	oxoguanine-DNA glycosylase-1
PGC-1α	peroxisome proliferator-activated receptor γ coactivator-1α
PPAR-1	peroxisome proliferator activated receptor-1
PI3K	phosphatidylinositol 3-kinase
p66shc	66 kDa Src homology 2 domain-containing protein
TFAM	mitochondrial transcription factor A
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
3-NT	3-nitrotyrosine
TINCR	Terminal differentiation-induced non-coding RNA
VDAC	voltage-dependent anion channel

the DOX quinone moiety and oxygen molecules and other cell electron donors, thereby resulting in DNA damage and lipid peroxidation [9,10]. DOX can trigger an inflammatory response by activating NF-κB and can upregulate inflammatory factors in H9c2 cells [11]. Recent studies have confirmed that cardiac fibrosis, senescence, and noncoding RNAs (ncRNAs) are also closely involved in DOX-induced cardiotoxicity. Nevertheless, the mechanism of DOX-induced chronic cardiotoxicity is still unclear, particularly lacking specific therapeutic targets, and how to use new drugs to protect cardiotoxicity without affecting antitumor effects is also the challenge. In addition, clinical trials of new drugs need to balance the risk of cardiac dysfunction caused by large doses of drugs and the harm caused by suspension of anti-tumor therapy [4], which hinder the development of novel drugs, so there is an urgent need for more studies from different perspectives to protect cardiotoxicity.

The key roles epigenetic mechanisms in complex diseases, including cardiovascular disorders, are clearly established. Epigenetics refers to the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states [12]. These chromatin-based modifications include DNA methylation, post-translational modifications, and RNA-based mechanisms [13]. Post-translational modifications in the nucleosome of chromatin and modified in N-terminal tails are emerging as vital epigenetic modulatory mechanisms, including acetylation, phosphorylation, ubiquitination, ADP-ribosylation, deamidation, and isomerization [14]. Acetylation is one of the most frequent modifications, taking place in approximately 85 % of eukaryotic proteins [15]. In the past 30 years, a prominent series of congruent observations has brought acetylation and related enzymes to the leading edge of research on cellular regulatory mechanisms [16].

Acetylation is a reversible, highly dynamic modification that neutralizes and reduces the charge of lysine residues and modifies protein structures, thus affecting DNA-binding affinity, enzymatic activity, protein stability, and subcellular localization [17,18]. It is involved in many cellular phenomena, such as gene transcription, mRNA splicing, signal transduction, and cell survival [19]. Acetylation homeostasis is the main epigenetic mechanism underlying cardiac dysfunction [20], and proteomics research has revealed acetylation involved in the modulation of diverse pathways and sites associated with cardiotoxicity through targeting HDACs and HATs (Table 1); this research provides a basis for the development of strategies to improve outcomes in patients undergoing chemotherapy [21]. In this review, we summarize recent achievements in our understanding of the protective mechanism and function of acetylation in DOX-induced cardiotoxicity. After a summary on programmed cell death, this review emphasizes the associations of acetylation with oxidative stress in the development and pathogenesis of cardiotoxicity. We further discuss the factors and potential drugs that influence HDACs and HATs to regulate therapeutic targets and signaling pathways aimed at preventing cardiotoxicity caused by DOX.

Table 1
HDACs and HATs involved in DOX-induced cardiotoxicity.

Classification	HDACs and HATs	Changes of HDACs and HATs in DOX-induced cardiotoxicity	HDACs and HATs involved in the treatment of DOX-induced cardiotoxicity	Ref
HDACs	HDAC1, HDAC2, HDAC3, HDAC8	HDAC1, HDAC2	HDAC6	[149, 153]
Class I HDACs	HDAC4, HDAC5, HDAC7, HDAC9	HDAC4, HDAC5, HDAC7	SIRT1, SIRT2, SIRT3, SIRT6	[149]
Class IIa HDACs	HDAC6, HDAC10	HDAC6, HDAC10	p300	[56, 149]
Class IIb HDACs	SIRT1, SIRT2, SIRT3, SIRT4	SIRT1, SIRT2, SIRT3, SIRT6		[27, 53, 106, 114]
Class III HDACs	SIRT5, SIRT6, SIRT7	HDAC11		[149]
Class IV HDACs	HDAC11	p300		[145, 154]
HATs p300/CBP family	p300, CBP			

2. Mechanism and function of acetylation in cardiotoxicity

2.1. Programmed cell death and acetylation in cardiotoxicity

2.1.1. Apoptosis

Apoptosis, a type of programmed cell death, is critical in organismal evolution, cell renewal, and internal environment stability [22]. Dunnione, a powerful substrate of NAD(P)H quinone oxidoreductase 1 (NQO1), increases cellular NAD + levels, alleviates cardiomyocyte apoptosis by restoring SIRT1 activity and negatively modulating acetylated p53, and ameliorates DOX-induced cardiac dysfunction and acute myocardial injury [23]. Rac1 is a key subunit of NADPH oxidase and mediates p53 acetylation by inhibiting HDACs activity to prevent DOX-induced apoptosis in H9c2 cells [24]. SIRT1 facilitates cell survival by deacetylating non-histone substrates, lysine 373 (Lys 373) and lysine 382 (Lys 382) of p53 to reduce its activity [25,26], which can downregulate the expression of the proapoptotic protein Bax, suppress the release of cytochrome *c*, and inhibit the activation of caspase-9 and caspase-3 [27]. Moreover, the downregulation of the molecular chaperone heat shock proteins 25 (HSP25) reduces the interaction between SIRT1 and p53, resulting in an increase in p53 acetylation on K379 to augment H9c2 cell apoptosis [28]. Of note, reduction of acetylated p53 can downregulate the IGF-1R/Akt pathway, and it is worth noting that IGF-1R could activate Akt, thereby promoting proliferation and regeneration in cardiac progenitor cells [25]. Melatonin exerts anti-apoptotic effect and maintains mitochondrial function through increasing the expression of SIRT1 and PGC-1α [29]. In addition, SIRT1 overexpression protects myocardial cells from apoptosis and oxidative stress by inhibiting p38MAPK phosphorylation and caspase-3 activation to ameliorate cardiotoxicity [30]. In general, SIRT1 can protect cardiomyocytes from DOX-induced apoptosis, as demonstrated in cells and in mouse and rat models; however, further studies are needed to determine its corresponding roles in humans.

SIRT3, shows strong deacetylase activity, with several mitochondrial targets that are critical for apoptosis, metabolism, mitochondrial fusion-fission dynamics, and detoxification [31,32]. SIRT3-mediated Ku70 deacetylation enhances its interplay with Bax, thus disturbing the pro-apoptotic translocation to mitochondria [33]. SIRT3 protects against DOX-mediated cell death and blocks mitochondrion-mediated apoptosis by the deacetylation of OPA1 at lysine 926 and 931 residues, and OPA1 is a GTPase immobilized on the inner mitochondrial membrane, which participates in mitochondrial fusion [34]. It is speculated that delayed toxicity may be related, in part, to a decrease in SIRT3 levels with age; accordingly, the maintenance of mitochondrial SIRT3 levels is essential to protect against cardiotoxicity [35].

The JAK/STAT signal transduction pathway regulates cell survival

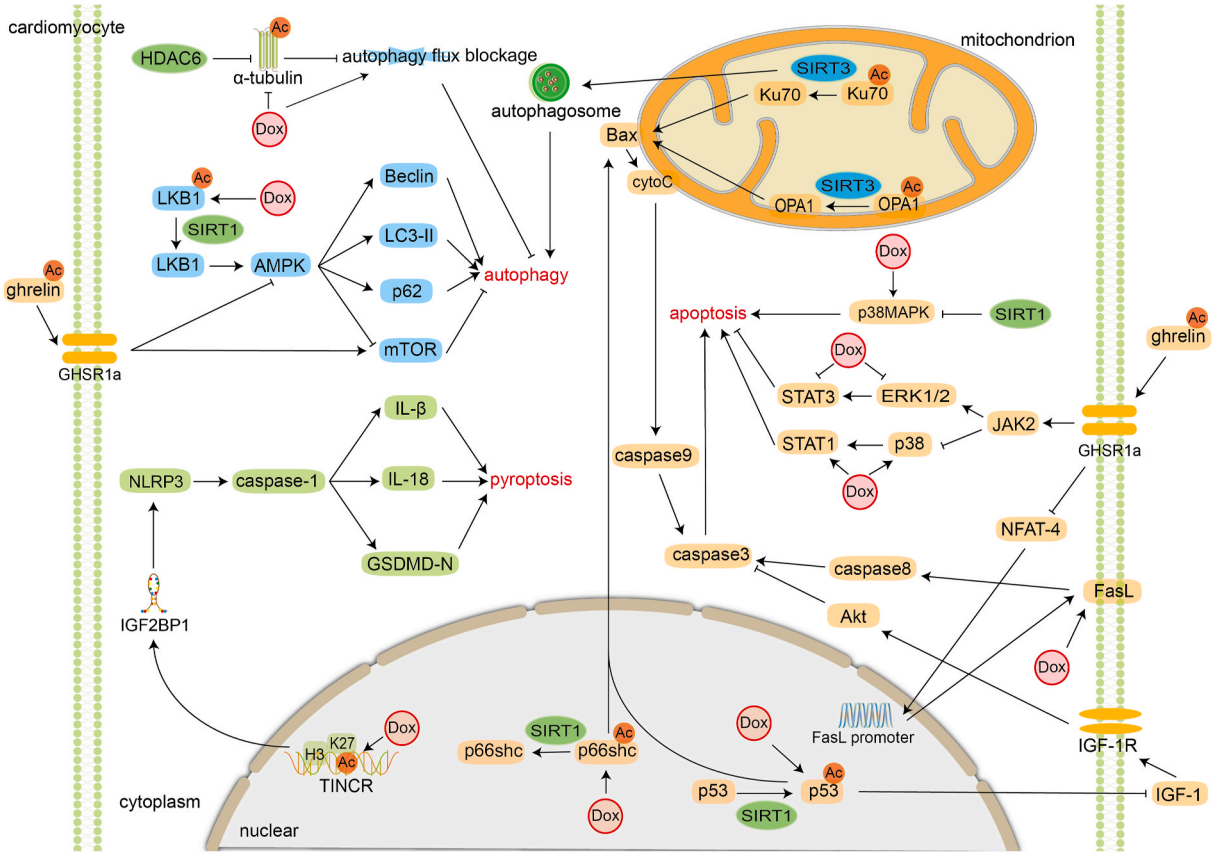

Fig. 1. The regulation of acetylation in DOX-induced programmed death of cardiomyocytes.
DOX increases p53 expression and induces Bax upregulation, subsequently triggers cytochrome *c* release, promotes caspase-9 and caspase-3 in sequence, and p53 also inhibits IGF/Akt signaling to increase caspase-3 levels. SIRT1-mediated deacetylation of p53 and p66shc reverses the above process via inhibiting Bax expression and SIRT1 inhibits p38MAPK activity, which alleviate DOX-induced apoptosis. Sirt3 deacetylates Ku70 and OPA1, leading to reducing Bax expression and mitochondria proapoptotic translocation. In addition, DOX inhibits STAT3 and ERK1/2, activates STAT1 and p38, acylated ghrelin prevents apoptosis through activation of STAT3 and inhibition of STAT1, which depends on GHSR1a receptors and requires JAK2 activation, and acylated ghrelin inhibits NFAT-4 nuclear translocation and downregulates FasL to reduce the expression of caspase-8 and caspase-3. Acylated ghrelin also suppresses excessive autophagy through inhibiting AMPK and stimulating p38-MAPK and mTOR. SIRT1 inhibits the mTOR pathway and activates Beclin1, LC3-II, p62 to promote autophagy, and SIRT3 induces the production of autophagosome and promotes autophagy. HDAC6 inhibitors recovers DOX-induced autophagy flux blockage through increasing α-tubulin acetylation. DOX upregulates TINCR via enhancing histone acetylation (H3K27ac) at promoter region and TINCR enhances NLRP3 activation and promotes the expression of caspase-1, IL-1β, IL-18 and GMDSD-N via bending with IGF2BP1, knockdown of TINCR attenuates the DOX-induced pyroptosis [7].

and apoptosis in the mammalian heart. DOX transfers the normal cardiac signal from JAK2/STAT3 to JAK2/STAT1 and subsequently induces cardiac intrinsic apoptosis and fibrosis. Interestingly, Eid and colleagues have shown that acylated ghrelin has cardioprotective effects via the activation of STAT3 and inhibition of STAT1 in rats, and this process is mediated by the receptor GHSR1a and activation of JAK2 [36,37]. Acylated ghrelin also inhibits NFAT-4 nuclear translocation to downregulate Fas and FasL, upregulate SERCA2a, and increase the activity of PKA and Akt, resulting in the inhibition of extrinsic cell death and restoration of normal Ca homeostasis [38] (Fig. 1). However, a number of studies have shown that a high dose of acylated ghrelin may have side effects, including endocrine and sympathetic nervous system symptoms [39,40]. Therefore, further clinical studies are needed to test the safety of acylated ghrelin in patients with cancer. In addition, the increase of H3K9ac levels in the transcription initiation region of Pik3ca stimulate the transcription of Pik3ca, subsequently activating PI3K/Akt pathway to promote apoptosis of H9c2 cells, which provides a new theoretical basis for the study of DOX-induced cardiotoxicity [41].

2.1.2. Pyroptosis

Different from apoptosis and necrosis, pyroptosis is a form of programmed cell death characterized as pro-inflammatory [42]. The process is regulated by pyrolytic caspases, including caspase-1, - 4, - 5, and –11, and activating caspase-1 can convert IL-1β, IL-18, and GSDMD in the plasma into active forms [43]. Terminal differentiation-induced non-coding RNA (TINCR) is a function-specific and tissue-specific lncRNA spliced from a 3.7 kb transcript, whose promoter region is highly enriched in histone acetylation (H3K27ac). The adaptor protein IGF2BP1 distributed in the cytoplasm of cardiomyocytes together with TINCR cooperatively affect the stability, translatability, and localization of mRNA [44,45]. DOX can enhance the binding and modification of H3K27ac in the promoter region of TINCR; this results in the up-regulation of TINCR, increases in NLRP3 expression at the mRNA and protein levels by the recruitment of IGF2BP1, and modulation of cardiomyocyte pyroptosis (Fig. 1). The knockdown of TINCR, silencing of IGF2BP1, and application of the NLRP3 inhibitor MCC950 reverse the increases in NLRP3, caspase-1, IL-β, IL-18, and GSDMD-N to eliminate DOX-induced H9c2 cell pyroptosis. However, the process by which DOX-activated TINCR guided IGF2BP1 to increase NLRP3 expression has no effect on DOX-induced apoptosis or pyroptosis in cancer cells [7]. Further studies of the role of TINCR/IGF2BP1/NLRP3 signaling pathway in DOX-induced cardiotoxicity are needed to improve our understanding of DOX-mediated pyroptosis in myocardial cells and to develop new anticancer strategies aimed at preventing cardiotoxicity.

2.1.3. Autophagy

Autophagy is a series of reactions in eukaryotic cells to degrade unnecessary or damaged cell components and proteins [46]. There is strong evidence that DOX blocks autophagic flux in the heart, and cardiomyocytes can control injury and restore energy homeostasis via autophagy and survival mechanisms after stress stimuli, such as DOX [47]. p62 and LC3-II are autophagic target and can be affected transcriptionally by stress (including doxorubicin), therefore DOX can increase p62 protein levels and promote LC3-II accumulation in cardiomyocytes to block autophagic flux. SIRT1 can restore V-ATPase activity and lysosomal acidification and improve autophagy by various mechanisms [48]. SIRT1 deacetylates FOXOs to control autophagy-related genes to increase autophagic flux, and inhibition of mTOR can reduce phosphorylation of TFEB at the lysosomal surface and induce nuclear localization of TFEB via mutation of serine 211 to non-phosphorylatable residues. After TFEB is activated, lipolysis is increased via lipophagy-mediated utilization of liposomal, and cellular ability to respond to lipid signals is also enhanced [49,50]. In addition, the blockage of autophagic flux prevents the proper removal of damaged organelles and unprocessed proteins caused by oxidant stress, thus aggravating heart injury [51,52]. Coelho and colleagues have suggested that Berberine promotes protective autophagy by preventing the accumulation of damaged proteins and has opposing effects on autophagy depending on the concentration [53]. Accordingly, increasing autophagic flux is promising for the reduction of DOX-induced cardiotoxicity.

DOX may affect microtubule structure, microtubule organization, and microtubule-related proteins [54]. Acetylated α-tubulin plays a vital role in stabilizing mitochondrial membrane potential and maintaining mitochondrial morphology and function [55]. Song et al. found that conserved cardiac function, autophagy flux, and mitochondria function in DOX-treated HDAC6-knockout mice are partially inhibited by colchicine and nocodazole, which decrease α-tubulin acetylation in neonatal rat cardiomyocytes [56]. Furthermore, the inhibition of HDAC6 can prevent cardioprotein toxicity by α-tubulin hyperacetylation-induced autophagy, and increases in acetylated α-tubulin can improve the assembly of the autophagy cargo along microtubules and rescue the DOX-induced inhibition of autophagy flux [21,57]. Acylated ghrelin has a similar function in autophagy to that of acetylated α-tubulin. Acylated ghrelin inhibits excessive autophagy by inhibiting AMPK and stimulating p38-MAPK and mTOR [58] (Fig. 1).

2.1.4. Iron metabolism

Many studies have found that ferroptosis plays an important role in the development of cardiotoxicity, and doxorubicin forms chelates with iron, which can undergo redox cycles to generate oxygen free radicals, and can also be combined with cardiolipin to destroy cell membrane function. Reducing mitochondrial iron levels can prevent dox-induced cardiotoxicity., whether acetylation can participate in ferroptosis needs further research [59]. Although programmed deaths have played pivotal roles in chronic DOX-induced cardiotoxicity, the exact mechanism needs to be further explored to help researchers find and develop effective targeted drugs.

2.2. Oxidative stress and acetylation in cardiotoxicity

Cardiotoxicity is closely related to oxidative stress caused by ROS, antioxidant depletion, and lipid peroxidation. Epigenetic modulators can improve the redox state and ROS levels [60]. SIRT1 exerts protective effects on DOX-induced cardiomyocyte toxicity and mitochondrial biogenesis dysfunction. Notably, PGC-1α is deacetylated via SIRT1 to activate mitochondrial biogenesis-related genes [30]. Pterostilbene upregulates PGC1α by enhancing SIRT1 activity and activating AMPK to inhibit DOX-induced oxidative stress and mitochondrial damage [61]. Furthermore, the hematopoietic cytokine erythropoietin (EPO) increases the expression and activity of SIRT1 and activates endothelial NO synthase (eNOS) and the PGC-1α-related transcriptional network to protect cardiomyocytes from oxidative stress [62]. p66Shc is a key intracellular mediator that modulates redox balance via increasing ROS concentration and promotes mitochondrial oxidative signals into apoptosis, and SIRT1 decreases the binding of the p66shc promoter region to acetylated histone H3 to inhibit the activity of p66shc [63,64]. Furthermore, berberine pretreatment can increase SIRT1 expression to downregulate p66shc to circumvent DOX-induced cardiotoxicity. Berberine also enhances the activity of GSH-PX, reduces levels of MDA in vivo, and regulates intracellular $\Delta\Psi m$ and $[Ca^{2+}]$, subsequently ameliorating DOX-induced oxidative stress and mitochondrial damage [63]. In addition, Nrf2 is a key antioxidant sensor that maintains redox homeostasis. Increasing Sirt1 expression and the Sirt1-dependent activation of pAMPK can restore the protein abundance and cardiac nuclear accumulation of Nrf2, recover levels of the downstream factors catalase (CAT), superoxide dismutase (SOD), heme oxygenase 1 (HO-1) [65], and activate antioxidant enzymes to reduce DOX-induced oxidative stress [66]. These processes are augmented by fibroblast growth factor 21 (FGF21) and acacetin by restoring the antioxidant capacity of Nrf2 [67]. Moreover, METRNL, a newly identified myokine, and Oroxylin A, a natural flavonoid, both activate SIRT1 via the cAMP/PKA signaling axis

to alleviate oxidative stress [66,68]. Sirt2 regulates oxidative stress by upregulating FOXO3a and MnSOD [69]. Adp355 has a similar therapeutic effect to that of adiponectin, which can attenuate levels of Nrf2, PGC-1α, Sirt2, and FOXO3a to eliminate DOX-induced myocardial oxidative damage [70].

Recently, SIRT3 has been reported to protect mitochondria from oxidative stress. Its overexpression promotes to contain the elevated ROS and protects the heart from toxicity by preventing mitochondrial DNA (mtDNA) damage via the oxidation of guanosine nucleotides and the accumulation of 8-oxo-dG adducts [35]. Oxoguanine-DNA glycosylase-1 (OGG1) can block mtDNA damage, and mitochondrial fusion is another approach to maintain mtDNA integrity [71]. SIRT3 can bind to OGG1 to promote its deacetylation and stabilization in cardiomyocytes; it also contributes to a decrease in fibrosis following transaortic constriction [72]. Furthermore, SIRT3 regulates ROS production by deacetylating and activating isocitrate dehydrogenase 2 (IDH-2), which consumes NADPH to convert oxidized glutathione to glutathione in response to DOX [73]. SIRT3 could also deacetylate MnSOD and SOD2 to prevent mitochondrial disruption caused by oxidative stress in cardiomyocytes [35,74]. In addition, Bcl-2-like 19 kDa-interacting protein 3 (Bnip3) is a vital regulator of cardiomyocyte mitochondrial function during DOX-induced cardiomyopathy [75]. Bnip3 overexpression abrogates the preservation of Cox1–Ucp3 complexes and completely blocks the attenuation of mitochondrial perturbations by SIRT3, such as mPTP opening, loss of ΔΨm, and mitochondrial ROS production; Bnip3 inhibition therefore restores mitochondrial integrity and respiratory capacity via SIRT3, implying a protective function against myocardial hypertrophy and mitochondrial dysfunction [76,77], and the disruption of mitochondrial dynamics may be related to mtDNA damage and delayed cardiotoxicity. Interestingly, the circadian oscillation of SIRT3 activity is regulated by the rhythmic biosynthesis of NAD + to control mitochondrial function and oxidative stress, providing a basis for further studies of the optimal timing of SIRT3 administration to attenuate adverse effects [78–80].

The nuclear acetyltransferase p300 is a co-activator of multiple transcription factors [81], and participates in various cellular processes, including proliferation, differentiation, and signal-activated gene expression [82]. It exerts cytoprotective effects via its substrate and downstream effector STAT3. DOX induces p300 protein amplification and acetylation in cardiac myocytes; the increase in p300 protects against oxidative stress to promote cardiomyocyte survival by the acetylation, activation, and stabilization of STAT3, and upregulation of MnSOD [83] (Fig. 2). In addition, as a histone acetyltransferase inhibitor, curcumin attenuates DOX-induced cardiotoxicity by scavenging free radicals and inhibiting lipid peroxidation, and protects against cardiac injury by membrane stabilization [84,85]. As described above, several natural products (e.g., honokiol and berberine) are promising for preventing cardiotoxicity; further research should focus on the mechanisms

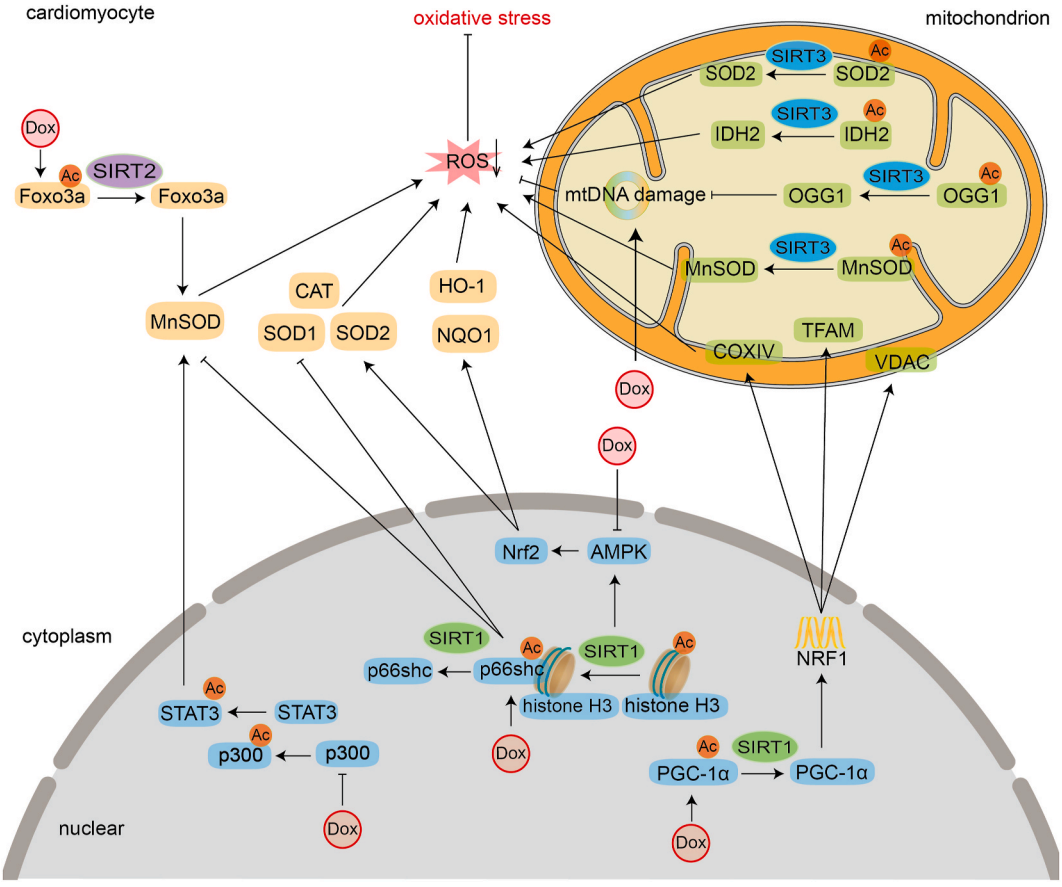

Fig. 2. The regulation of acetylation in DOX-induced oxidative stress.
Increasing SIRT1 activity and AMPK expression reverses DOX-induced acetylation of PGC-1α and suppression of PGC-1α-related genes involved in mitochondrial biogenesis and ROS accumulation such as NRF1, TFAM, COXIV and VDAC. SIRT1 decreases acetylated histone H3 binding to the p66shc promoter region and represses p66shc activity, thereby reversing DOX-induced p66shc activation and downregulation of CAT, SOD and MnSOD. Sirt1-mediated activation of AMPK/Nrf2 signal counters the reduction of HO-1, NQO1, SOD1 and SOD2 caused by DOX, thus decreasing ROS production and attenuating oxidative stress. In addition, SIRT2 activates Foxo3a and upregulates MnSOD levels to reduce DOX-induced Foxo3a inhibition and oxidative stress. SIRT3 repairs mtDNA damage caused by DOX via deacetylating and increasing activity of OGG1, and Sirt3-mediated deacetylation of MnSOD, SOD2 and IDH2 regulates ROS production and protects oxidative stress. DOX induces p300 acute amplification, and elevated p300 protect oxidative stress via acetylation and activation of STAT3. Inhibition of HDAC6 reduces DOX-induced oxidative stress by promoting p300 acetylation.

underlying the regulation of SIRTs and their clinical applications.

Inflammation is positively correlated with oxidative stress in myocardial injury. NF-κB, a critical regulator of inflammatory responses, is modulated by post-translational modifications (mainly acetylation) and controls the expression of multiple pro-inflammatory chemokines and cytokines involved in cardiotoxicity [86,87]. Recent studies have demonstrated that SIRT1 physically interacts with and deacetylates nuclear NF-κB p65 at the lysine-310 subunit to inhibit NF-κB transcriptional activity and inflammatory mediators [88,89]. The LKB1/AMPK axis is a highly sensitive target of DOX-induced cardiac injury and SIRT1 binds to and reduces LKB1 acetylation, thereby promoting AMPK activation and improving inflammation and oxidative stress. C1q/tumor necrosis factor-related protein-3 (CTRP3) and Dunnione alleviate DOX-induced inflammatory response by facilitating SIRT1 activation to suppress the acetylation of NF-κB p65 and production of inflammatory cytokines, such as TNF-α, IL-6, IL-1β and MCP-1 [23,90]. As an important regulator of lipid and glucose metabolism, FGF21 can abolish the nuclear translocation of NF-κB p65 and exert anti-inflammatory effects via the SIRT1/LKB1/AMPK pathway [91] (Fig. 3). Roflumilast can also suppress the secretion of inflammatory factors and attenuate cardiomyocyte inflammation by upregulating SIRT1 [92]. In addition, curcumin ameliorate DOX-mediated cardiac hypertrophy through the disruption of the p300-HAT activity [93]. NLRP3, a modulator of the innate immune system, is activated in response to danger signals caused by diseases and infections and has been implicated in DOX-induced cardiotoxicity [94]. Calycosin (CA) prevents the activation of NLRP3, TXNIP, IL 1β, and caspase 1 in the presence of DOX, and Dihydromyricetin (DHM) markedly upregulates SIRT1 expression to inhibit the DOX-induced activation of NLRP3, thereby alleviating apoptosis and inflammation in H9C2 cells and rats [95,96]. Of note, PPARγ-specific ligands have anti-inflammatory effects in the cardiovascular system, honokiol treatment protects DOX-induced mitochondrial dysfunction and reduce oxidative stress and inflammation via enhancing PPARγ transcriptional activities [97]. The various above-mentioned activators that alleviate DOX-induced cardiotoxicity by targeting HDACs and HATs are listed in Table 2.

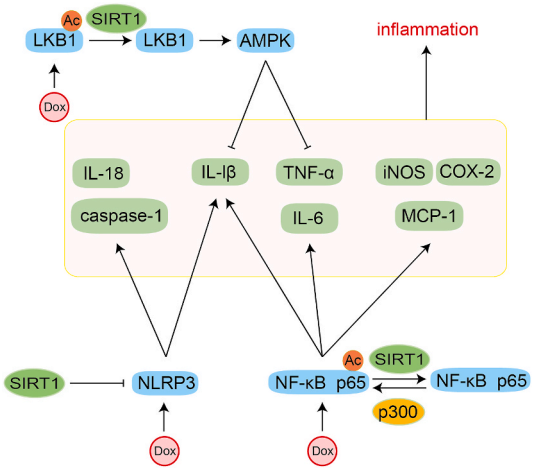

Fig. 3. The regulation of acetylation in DOX-induced inflammation.
DOX promotes the nuclear translocation of NF-κB p65 to increase the expression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and chemokines (iNOS, COX-2 and MCP-1). SIRT1 deacetylates the NF-κB subunit p65 and blocks NF-κB-dependent inflammatory responses, whereas p300 overexpression reverses the SIRT1-induced inhibitory effects on NF-κB signal. SIRT1 binds to LKB1 and decreases LKB1 acetylation, subsequently inducing AMPK activation to reduce the levels of TNF-α, IL-6, IL-1β, which reverses the inhibition of LKB1/AMPK signaling induced by DOX. Moreover, DOX promotes the NLRP3 inflammasome activation, then increasing the release of caspase1, IL-1β and IL-18. SIRT1 reduce acetylation of NLRP3 and inhibit NLRP3 inflammasome activation, thus alleviating DOX-induced inflammation.

3. Noncoding RNAs (ncRNAs) and acetylation in cardiotoxicity

3.1. MicroRNAs (miRNAs) and acetylation in cardiotoxicity

MiRNAs are a type of regulatory small non-coding RNAs, which have been reported to be involved in multiple biological activities [98–100]. MiR-34a, an important regulator in cardiac diseases and repair, is involved in several cellular processes. The systemic delivery of Ant34a to DOX-treated rats can upregulate the cardiac expression of Bcl-2 and downregulate TGF-β pathway via SIRT1 activation, thus moderating myocardial apoptosis and fibrosis. Of note, miR-34a is involved in the modulation of DNA damage responses and telomere maintenance, providing a potential mechanism for senescence and inflammation. In addition, Ant34a has protective effects against refractory preserved diastolic dysfunction, an early sign of cardiotoxicity [101]. Furthermore, miR-34a-5p increases p66shc expression, while Sirt1 deacetylates histone H3 lysine 9 binding to the p66shc promoter region, thus reducing the levels of p66shc, Bax, and caspase-3 to alleviate DOX-induced cardiomyocyte apoptosis [102]. Therapeutic inhibition of miR-34a may have clinical relevance to alleviate DOX-induced cardiotoxicity, and further studies are needed to confirm that blockage of miR-34a-5p/Sirt1/p66shc pathway representing a potential cardioprotective method.

MiR-22, a key regulator of stress-induced heart damage, directly binds to the 3′-UTR and downregulates SIRT1. MiR-22 antagomir increases resistance to oxidation in the heart and suppresses cardiomyocyte apoptosis and oxidative stress by upregulating SIRT1 [103]. MiR-22 levels are positively correlated with MDA levels and negatively related to the GSH (glutathione)/GSSG (glutathione disulfide) ratio reflecting redox status in the myocardium, implying that it regulates cardiac oxidative stress [104]. Furthermore, inhibition of miR-200a-3p attenuate DOX-induced apoptosis and inflammation of cardiomyocytes through targeting paternally expressed gene 3 (PEG3) to regulate Sirt1-mediated deacetylation of p53 and NF-κB p65 [105]. Moreover, miR-140-5p antagomir alleviates oxidative stress in cardiomyocytes by targeting Nrf2 and SIRT2 pathway to bind with antioxidant-response elements (ARE), and increase FOXO3a and decrease ROS levels [106].

3.2. Long noncoding RNAs (lncRNAs) and acetylation in cardiotoxicity

NEAT1, a lncRNA transcribed from NEAT1, is vital for gene stability. It participates in mRNA conditioning networks via competing endogenous RNA (ceRNA)-mediated miRNA evasion. MiR-221-3p is a target ceRNA of NEAT1 and its enrichment in aged myocardial tissues could impair myocardium regeneration by suppressing the sirtuin family [107–109]. MiR-221-3p interacts with the 3′-UTR of Sirt2 to inhibit Sirt2 expression at the post-transcriptional level, and Sirt2 activates AMPK to attenuate age-related cardiac hypotrophy and DOX-induced cardiotoxicity, implying that the exosome/NEAT1/miR-221-3p/Sirt2 pathway attenuates cardiomyocyte senescence [110,111].

3.3. Circular RNAs (circRNAs) and acetylation in cardiotoxicity

CircITCH is a circRNA produced by the reverse splicing of exons 7–14 of the itchy E3 ubiquitin protein ligase (ITCH) gene, a tumor suppressor [112,113]. CircITCH, as a natural sponge of miR-330-5p, upregulates SIRT6, Survivin, and SERCA2a to attenuate DOX-induced cardiomyocyte damage and dysfunction. The CircITCH/miR-330-5p axis regulates DNA damage, cell/mitochondrial oxidative stress, cell death, calcium handling defects, and contractile dysfunction in DOX-treated human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) through the interaction of miR-330-5p with SIRT6, BIRC5, and ATP2A2. Mutations in the BIRC5 and ATP2A2 3′-UTRs can reverse the effects of miR-330-5p overexpression and CircITCH-silencing [114]. SIRT6 has recently been shown to alleviate oxidative stress by activating Nrf2 and SOD2, two key endogenous oxidative stress defense molecules

Table 2
Summary of activators targeting HDACs in DOX-induced cardiotoxicity.

Activators	HDACs	Functions	Mechanism	Cell or animal model	DOX dose, period	Ref
METRNL	SIRT1	Anti-apoptosis, antioxidation;	Activate cAMP/PKA pathway;	H9c2 cells;	1 μ mol/L, 24 h	[66]
CTRP3	SIRT1	Improve cardiac function	Increase Nrf2 expression	Male C57BL/6 mice	16 mg/kg, 4 weeks	[90]
FGF21	SIRT1	Anti-apoptosis, anti-inflammation;	Increase AMPKα expression;	H9c2 cells;	1 μ mol/L, 12 h	[91]
Acacetin	SIRT1	Improve cardiac function	Inhibit NF-κB expression	Male C57BL/6 mice	15 mg/kg, 4 weeks	[67]
Dihydromyricetin	SIRT1	Anti-apoptosis, antioxidation;	Activate LKB1/AMPK pathway	H9C2 cells;	5 μg/ml, 22 h	[95]
Calycosin	SIRT1	Anti-inflammation	Inhibit NF-κB expression	129S1/SyImJ mice	20 mg/kg, 4 weeks	[96]
Higenamine	SIRT1	Anti-apoptosis, antioxidation;	Activate pAMPK pathway;	H9c2 cells;	1 μM, 24 h	[155]
β-LAPachone	SIRT1	Improve cardiac function;	Increase Nrf2 expression	Male C57BL/6 mice	15 mg/kg, 4 weeks	[156]
		Improve myocardial fibrosis	Inhibit NLRP3 activation;	H9c2 cells;	5 μ mol/L, 24 h	
		Anti-apoptosis, anti-inflammation;	Inhibit PI3K-Akt expression;	Sprague Dawley rats	15 mg/kg, 6 weeks	
		Prevent cardiac tissue damage;	Increase antioxidant enzyme activity;	H9c2 cells;	5 μM, 24 h	
		Improve cardiac function	Inhibit NLRP3 activation	Male Kunming mice	15 mg/kg, 7 days	
		Anti-apoptosis, antioxidation;	Activate LKB1/AMPK α1 pathway	H9C2 cells	5 μ mol/L, 24 h	
		Anti-inflammation;	Activate LKB1/AMPK/Nrf2 pathway	Sprague Dawley rats	15 mg/kg, 7 days	
		Protect mitochondrial function		C57BL/6 mice	15 mg/kg, 2 weeks	
		Improve cardiac function;				
		Improve chronic heart failure				
		Anti-apoptosis, antioxidation;				
		Anti-inflammation;				
		Ameliorate autophagy;				
		Improve cardiac function				
Activators	HDACs	Functions	Mechanism	Cell or animal model	DOX dose, period	Ref
Pterostilbene	SIRT1	Antioxidation;	Activate PGC-1α/AMPK pathway	H9c2 cells;	1 μM, 24 h	[61]
		Protect mitochondrial damage;		Male C57BL/6 mice	20 mg/kg, 7 days	
		Alleviate cell viability inhibition				
Melatonin	SIRT1	Anti-apoptosis;	Increase PGC-1α expression;	H9c2 cells;	3 μM, 24 h	[29]
Sesamin	SIRT1	Improve cardiac function;	Increase Mfn1, Mfn2 levels;	Sprague Dawley rats	12 mg/kg, 2 weeks	[157]
Dunnione	SIRT1	Regulate mitochondrial fusion, fission	Decrease Drp1, hFis1 levels	H9c2 cells;	2 μM, 24 h	[23]
Erythropoietin	SIRT1	Antioxidation;	Upregulate Mn-SOD activity	Sprague Dawley rats	20 mg/kg, 10 days	[62]
HSP25	SIRT1	Alleviate mitochondrial damage	Inhibit p53, NF-κB p65 expression;	H9C2 cells;	1 μM, 24 h	[28]
Roflumilast	SIRT1	Anti-apoptosis, anti-inflammation;	Attenuate PARP-1 hyperactivation	C57BL/6 mice	12 mg/kg, 7 days	[92]
Oroxylin A	SIRT1	Improve cardiac function;	Inhibit PGC-1α expression	AC16 cells	125 nM, 24 h	[68]
Dioscin	SIRT2	Ameliorate acute myocardial injury	Inhibit p53 expression	H9C2 cells	1 μ mol/L, 24 h	[158]
		Protect mitochondrial function	Inhibit IL-6, IL-17 secretion	H9c2 cells	5 μ mol/L, 24 h	
		Anti-apoptosis	Downregulate p21, PAI-1 levels	H9c2 cells;	5 μ mol/L, 24 h	
		Anti-inflammation;	Activate cAMP/PKA pathway;	Male C57BL/6 mice	20 mg/kg, 15 days	
		Attenuate cellular senescence	Increase Nrf2 expression;	H9c2 cells;	5 μM, 24 h	
		Anti-apoptosis, antioxidation;	Inhibit NF-κB expression	Male C57BL/6 mice	15 mg/kg, 7 days	
		Anti-inflammation;	Activate Nrf2/FOXO3a pathway	Sprague Dawley rats	15 mg/kg, 7 days	
		Alleviate cardiac injury;				
		Improve cardiac function				
		Antioxidation;				
		Alleviate myocardial injury				
Activators	HDACs	Functions	Mechanism	Cell or animal model	DOX dose, period	Ref
ADP355	SIRT2	Anti-apoptosis, antioxidation;	Increase Nrf2 expression;	H9c2 cells;	1 μM, 24 h	[70]
Honokiol	SIRT3	Anti-inflammation;	Increase FOXO3a expression;	Male C57BL/6 mice	20 mg/kg, 4	[97]
Berberine	SIRT1;	Improve myocardial fibrosis;	Inhibit α-SMA, Col1-α1 expression	H9c2 cells;	weeks	[53,
	SIRT3	Ameliorate cardiac atrophy;	Inhibit mitochondrial protein acetylation; Enhance PPARγ	Male C57BL/6 mice	5 μM, 24 h	63]
		Improve cardiac function	activity	H9c2 cells;	15 mg/kg, 45	
		Anti-apoptosis, antioxidation;	Inhibit p66shc, p53 expression;	Sprague Dawley	days	
		Anti-inflammation;	Inhibit OPA1 expression;	rats	1 μM, 24 h	
		Protect mitochondrial	Activate AMPK signal;	H9c2 cells	20 mg/kg, 10	
		respiration;	Inhibit PGC-1α expression;		days	
		Improve cardiac function	Increase TOM2, LC3-II, p62 content		1 μM, 24 h	
		Anti-apoptosis, antioxidation;				
		Protect mitochondrial function;				
		Modulate autophagy,				
		mitophagy;				
		Alleviate cardiac injury				

[115,116]. It also improves DNA damage by activating PARP1, which is involved in DNA damage repair [117,118]. CircITCH-miR-330-5p-SIRT6/BIRC5/ATP2A2 ceRNA network can reduce the cardiotoxicity of chemotherapy while potentiating tumor suppression and is therefore promising for DOX-based chemotherapy [114] (Fig. 4). These ncRNAs that target HDACs to regulate related pathways of DOX-induced cardiotoxicity are listed in Table 3. Other types of ncRNAs, such as tsRNAs and piRNAs, are playing an increasingly important role in heart disease [119–121], and whether they can target acetylation to protect against cardiotoxicity needs to be further explored. Multiple mechanism research and clinical verification are needed to realize the therapeutic potential.

4. Exercise and acetylation in cardiotoxicity

In an interesting recent discovery, aerobic exercise has been identified as a non-pharmacological approach to prevent DOX-induced cardiotoxicity [122]. Exercise influences epigenetic modifications

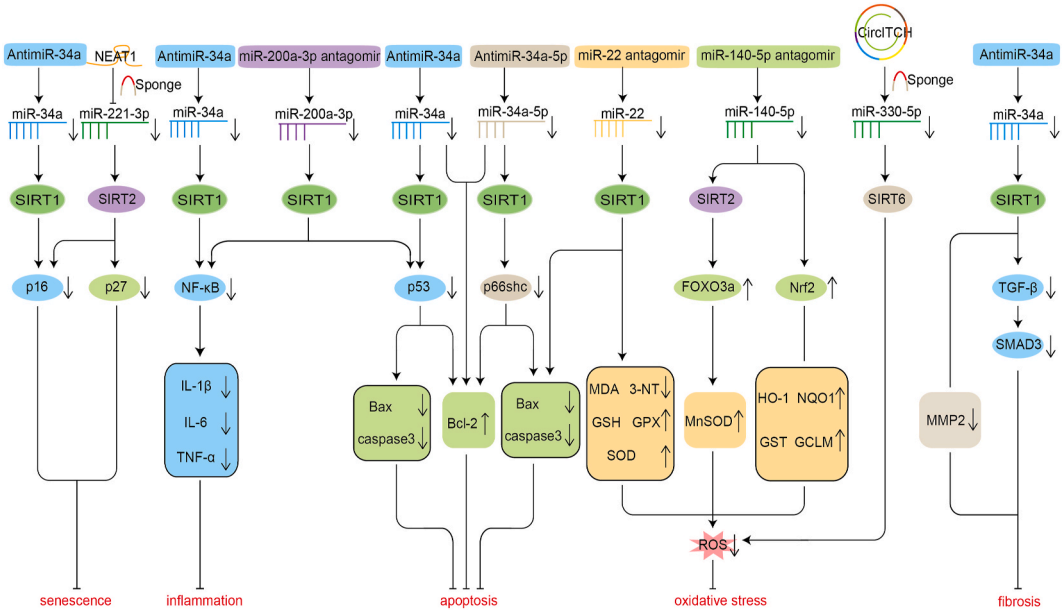

Fig. 4. Representative ncRNAs involved in the regulation of DOX-induced cardiotoxicity via targeting HDACs with animal or clinical evaluation.
AntimiR-34a and antimiR-34a-5p target and upregulate Bcl-2 collectively and increase SIRT1 activity to inhibit p53 and p66shc respectively, subsequently downregulating Bax and caspase-3 to attenuate DOX-induced apoptosis. MiR-22 antagomir mediates SIRT1 to reduce apoptosis, decrease the levels of MDA, 3-NT and increase the levels of GSH, GPX and SOD. MiR-140-5p antagomir targets Nrf2 to increase the expression of HO-1, NQO1, GST and GCLM, also targets SIRT2 to activate FOXO3a and upregulate MnSOD. CircITCH acts as sponge and sequesters miR-330-5p to increase SIRT6 activity, both miR-22 antagomir, miR-140-5p antagomir and CircITCH reduce ROS production and alleviate DOX-induced oxidative stress. AntimiR-34a inhibits NF-κB signaling and reduces the levels of TNF-α, IL-6, IL-1β to attenuate DOX-induced inflammation, also inhibits TGF-β/SMAD3 signaling and decreases MMP2 to attenuate DOX-induced fibrosis. AntimiR-34a targets SIRT1 to inhibit p16, NEAT1 acts as sponge and sequesters miR-221-3p to target SIRT2, then reducing the expression of p16 and p27 to attenuate DOX-induced senescence.

Table 3
Summary of ncRNAs targeting HDACs in DOX-induced cardiotoxicity.

NcRNA	HDACs	Functions	Target gene	Cell or animal model	DOX dose and treatment period	Ref
miR-34a	SIRT1	Reduce apoptosis;	p53	Male Sprague Dawley rats	15 mg/kg, 2 weeks	[101]
miR-34a-5p	SIRT1	Alleviate inflammation;	NF-κB p16	H9c2 cells;	5 μM, 24 h	[102]
miR-22	SIRT1	Reduce cell senescence;	TGF-β	Male Sprague Dawley rats	16 mg/kg, 4 weeks	[103]
miR-200a-3p	SIRT1	Improve fibrosis;	p66shc	H9c2 cells	1 μM, 24 h	[105]
NEAT1/miR-221-3p	SIRT2	Attenuate cardiac dysfunction	p53	Male Sprague Dawley rats	16 mg/kg, 4 weeks	[111]
miR-140-5p	SIRT2	Reduce apoptosis	p53	H9c2 cells;	2 μM, 24 h	[106]
CircITCH/miR-330-5p	SIRT6	Reduce apoptosis;	NF-κB	Male Wistar rats	24 mg/kg, 2 weeks	[114]
		Alleviate oxidative stress;	p27	Male C57/Bl6 mice	12 mg/kg, 1 weeks	
		Attenuate cardiac dysfunction	p16	H9C2 cells;	5 μM, 24 h	
		Reduce apoptosis;	FOXO3a	Male C57BL/6 J mice;	15 mg/kg, 8 days	
		Alleviate inflammation;	Nrf2	Male Sprague Dawley rats	15 mg/kg, 8 days	
		Promote cell proliferation	BIRC5	HiPSC-CMs	0.5 μM and 1 μM, 24 h	
		Alleviate cardiac injury;	ATP2A2			
		Reduce cell senescence				
		Alleviate oxidative stress				
		Reduce cell death;				
		Abrogate calcium handling defects;				
		Alleviate oxidative stress;				
		Alleviate DNA damage				

associated with cardiovascular disease via a series of specialized enzymes (such as HDACs), metabolites, and signaling pathways [123]. For example, myokine, FGF21, osteocrin, and fibronectin type III domain-containing 5 (FNDC5), all of which are related to exercise, significantly decrease apoptosis and oxidative damage in DOX-treated hearts and cardiomyocytes [91,124,125], and their effects are related to acetylation. Aleixo et al. demonstrated that a chronic physical exercise model before and during sub-chronic DOX treatment can improve mitochondrial function, and prevent mitochondrial damage and imbalance of redox homeostasis, indicating that upregulation of SIRT3 and downregulation of p66shc are involved in the mitochondrial protective phenotype associated with exercise; further studies should clarity the protective effects of the intensity and type of exercise on the heart [126,127]. Together with other sirtuins, Sirt6 activity is related to the level of NAD+, which acts as a metabolic sensor, and is upregulated during exercise. In response to DOX, Sirt6 stimulates DNA repair. It physically interacts with PARP-1 to increase its activity, deacetylates the C-terminal binding protein-interacting protein (CtIP) for DNA end-resection, and recruits SNF2H to open the condensed chromatin and maintain genome stability. Interestingly, the protective effects of exercise on progeny during pregnancy on DOX-induced cardiotoxicity are related to the inhibition of cell apoptosis and increased antioxidant defense [128].

5. Potential drug for acetylation in cardiotoxicity

5.1. SIRT activators

SIRT activators (e.g., Nicotinamide riboside, silybin, resveratrol) has been carried out in many clinical trials and achieved expected results in heart diseases such as coronary heart disease and heart failure. Meanwhile, many animal studies have shown their protective effects on DOX-induced cardiotoxicity. Nicotinamide riboside (NR) (a pan-sirtuin activator) is a pyridine-nucleoside form of vitamin B3 and is converted to NAD + via NR kinases 1/2 and nicotinic acid mononucleotide adenylyltransferase. Recent studies have provided strong evidence that NR improves autolysosome clearance, activates NAD+/SIRT1 signaling, and restores lysosomal acidification to prevent the accumulation of autolysosomes, the blockage of autophagic flux, and oxidative stress in DOX-treated cardiomyocytes. NR can alleviate necroptosis by inhibiting the release of LDH and preventing the phosphorylation of RIP3 and MLKL [52]. Given that NR is an effective dietary supplement with favorable safety, it is a potential drug candidate for clinical trials. Moreover, silybin (SLB) (a SIRT3 activator) is a strong antioxidant, concurrent administration of SLB and DOX with hepatic-targeting liposomes can attenuate DOX-induced acute cardiotoxicity via the inhibition of antioxidants, free radical scavenging, and lipid peroxidation [129].

Honokiol (putative sirt3 activator), reverses the DOX-induced hyperacetylation of MnSOD to prevent ROS production, and reduces 8-oxo-dG levels and maintains OGG1 levels to protect against mitochondrial damage. Moreover, Honokiol can protect from DOX-induced cardiac hypertrophy without affecting anticancer activity of doxorubicin [130]. In recent years, the protective effect of botanicals such as Honokiol on DOX-induced cardiotoxicity has become a research hotspot, and relevant clinical trials will gradually be implemented. Resveratrol (a SIRT1 activator) is a non-flavonoid polyphenolic compound with comprehensive biological and protective effects [131]. Pretreatment with resveratrol could attenuate USP7-related catabolism/pro-apoptosis signaling by restoring Sirt1 activity, alleviate oxidative stress by the SIRT1-mediated deacetylation of histone H3, and inhibit p70S6K-mediated autophagy [132,133]. Resveratrol plays the key roles in restoring ER homeostasis and cell viability via SIRT1 activation and suppresses myocardial fibrosis by downregulating TGF-β and pSMAD3/SMAD3 pathway [134,135]. However, resveratrol can activate SIRT1 in vitro but cannot be achieved in vivo due to the poor water solubility and bioavailability, which limits the therapeutic efficacy after oral administration. Increasing research therefore focused on solid lipid nanoparticles to improve the bioavailability, and as drug delivery systems to enable its gradual release and proper distribution [136,137].

5.2. HDAC inhibitors

HDAC inhibitors show antitumor effects at a well-tolerated dose in both hematological and solid cancers, and regulate the post-transcriptional activity of proteins by inhibiting histone deacetylation, affecting chromatin condensation, cell differentiation and migration [138]. Cytotoxicity and DNA damage caused by HDAC inhibitors disproportionately affect cancer cells over normal cell lines [139]. As an emerging therapeutic strategy, extensive research has focused on the combined application of HDAC inhibitors and chemotherapy drugs. Notably, several HDAC inhibitors are reported to mitigate cardiotoxicity. The histone deacetylase inhibitory prodrug butyroyloxymethyl diethyl phosphate (AN-7) abrogates ROS production and cell death in cardiomyocytes and reduces the inhibitory effect of DOX on HO-1 and HIF-1α to attenuate inflammation, increase angiogenesis, and prevent left ventricular hypertrophy [140]. The short-chain fatty acid phenylbutyric acid significantly reduces DOX-induced elevations in serum LDH, CK, and myocardial tissue ultrastructural damage; it also upregulates MnSOD to increase the antioxidant capacity and prevent the decline in heart function [141]. The selective HDAC6 inhibitor Tubastatin A protects against DOX-induced acute cardiomyopathy without affecting tumor growth inhibition [56]. Some HDAC inhibitors have been approved by the FDA for clinical application and others are in preclinical studies.

6. Conclusions and perspectives

An increasing body of evidence supports the link between DOX-induced cardiotoxicity and acetylation. This review emphasizes the great potential of HDACs and HATs in attenuating changes in programmed cell death, oxidative stress and inflammation caused by DOX. Research on the potential interaction between HDACs and ncRNAs is only in a preliminary stage, and further studies of the relationships between other HDAC isoforms and ncRNAs in cardiotoxicity are needed. We also provide an overview of exercise involved in the regulation of several HDACs, providing new therapeutic targets. Additionally, many components of traditional medicines and phytochemicals have obvious effects on HDACs and HATs, especially in the sirtuin family, and are candidates for future research aimed at reducing the cardiac side effects of chemotherapy.

Cardiotoxicity research has increasingly focused on SIRT activators and HDAC inhibitors. Although the research community has made great efforts to understand the mechanism of the beneficial effects of resveratrol, the precise dosing, risks, and outcomes in humans remain uncertain [142], and it should be noted that effective agents able to prevent cardiotoxicity without influencing the anti-cancer effects are limited and are urgently needed. In addition, there is substantial evidence that HDAC inhibitors may be effective anti-cancer agents, particularly in combination with traditional chemotherapy drugs. SAHA can increase the entry and binding of top II inhibitors, which can change Topoisomerase (Top 2β) configuration to a closed-clamp form, thus preventing dox from binding to the Top 2β complex to ameliorate DOX-induced cardiotoxicity [143,144]. By enhancing the effects of p300, the addition of HDACs to DOX-containing regimens may have beneficial effects on safety and efficacy in breast cancer [145]. Therefore, multi-drug synergy and the identification of effective combinations are important areas for future research. Nonetheless, HDAC inhibitors can also induce arrhythmia, hypertrophy, and other types of cardiac damage. While exploring the pharmacological pathways and etiopathogenesis of HDAC inhibitors in cardiotoxicity, these side effects should be evaluated in the early stages of drug development. Furthermore, HDACs have diverse substrates and regulatory mechanisms, thus an improved understanding of the cardiac function of each HDAC subtype will improve the identification of selective and specific HDAC inhibitors to treat DOX-induced cardiotoxicity more effectively and safely.

Dexrazoxane is the only drug approved by the FDA to prevent cardiotoxicity, but there are still some clinical trials showing the risk of bone marrow suppression and secondary tumors, which affects its wide clinical application [146]. Numerous clinical trials are currently conducted to study the effects of cardiovascular drugs on DOX-induced cardiotoxicity, such as β-blockers and ACE inhibitors [147]. Carvedilol is a β-blocker with unique antioxidant properties and emerges as a strategy to prevent cardiotoxicity, but there are also clinical trials questioning its effectiveness. Some evidence suggested that antioxidants, rather than β-blocker, can prevent cardiotoxicity, but the antioxidant effect of carvedilol may not be sufficient in some cases [148]. In-depth study of acetylation will help to explore the impact of drugs on the occurrence and development of diseases from the perspective of molecular mechanisms, thereby promoting safer and more effective implementation of clinical trials.

Several studies suggested that low-dose DOX caused specific changes in the transcription profiles of some HDACs, which are significantly deregulated in DOX-treated murine hearts including HDAC2, HDAC4, HDAC5, HDAC6, HDAC7, HDAC10 and HDAC11 [149], indicating that regulating these HDACs may also have therapeutic potential for DOX-induced cardiotoxicity. Moreover, except for doxorubicin, recent

studies have shown that SIRT1 alleviates cyclophosphamide-induced cardiotoxicity via NF-kB, PARP1, p53 and FoxO1-related pathway [150], and SIRT3 promotes the sensitivity of sunitinib-induced cardiotoxicity through the GSTP1/JNK/autophagy pathway [151]. Therefore, it is speculated that the underlying mechanism of acetylation may also play an important role in protecting cardiotoxicity induced by other chemotherapeutic drugs.

Notably, acetylation represents a promising field of cardiotoxicity investigation, with broad prospects for the development of new targets for treatment based on cutting-edge epigenomics approaches. In addition, the roles of epigenetic modifications other than acetylation in transcriptional regulation have also attracted increasing attention. Succinylation and malonylation have been linked to cardiomyopathy and angiogenesis, respectively [152], further emphasizing the importance of epigenetics research for improving our understanding of cardiotoxicity. Expanding on these observations and carrying out further molecular analyses focused on epigenetic mechanisms contributing to cellular processes represent the major challenges for future research.

Author contributions

D.L. collected materials and wrote the manuscript. T.Y. X.C. and Y.Y. provided the idea. B.B., C.T. and R.S. are responsible for the schematic diagram within this article. T.Y., D.L., X.H. and S.W. helped with the final revision of the article. All authors reviewed the manuscript and approved the final manuscript.

This review summarizes the mechanism and protective effect of acetylation in doxorubicin-induced cardiotoxicity, and highlights therapeutic potential for cardiotoxicity by targeting histone deacetylases (HDACs) and histone acetyltransferases (HATs).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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