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Letter to the Editor

HDAC1 Inhibition and Ferroptosis in Cardiac Hypertrophy: Bridging Basic Science to Clinical Translation

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We read with great interest the article entitled 'Mocetinostat Ameliorates Pathological Cardiac Hypertrophy via Suppression of Ferroptosis Through Nrf2 Pathway' by Li et al. [1], which reported that the histone deacetylase 1 (HDAC1) inhibitor mocetinostat attenuates pathological cardiac hypertrophy by suppressing ferroptosis via activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. The authors provided compelling evidence that mocetinostat promotes Nrf2 acetylation and nuclear translocation, thereby upregulating antioxidant targets including solute carrier family 7 member 11 (SLC7A11), glutathione peroxidase 4 (GPX4), ferritin heavy chain 1 (FTH1), ferroportin (FPN), and heme oxygenase-1 (HO-1). This study adds to the growing body of evidence implicating HDAC1 as a critical regulator of ferroptosis in cardiovascular pathology, thus offering a promising therapeutic strategy for heart failure [2].

The findings by Li et al. [1] align with emerging mechanistic insights into the regulation of HDAC1-mediated ferroptosis. Recent work has shown that HDAC1 can act as both a transcriptional repressor and activator in ferroptosis control. For instance, a study of the Piezo1-Ca^{2+}-calcineurin-NFAT2-HDAC1-BHLHE40-SLC7A11 axis demonstrated that HDAC1 functions as an essential coactivator. Its deacetylase activity drives the expression of basic helix-loop-helix family member e40 (BHLHE40), which subsequently upregulates SLC7A11 and thereby suppresses endothelial ferroptosis [3]. This suggests the role of HDAC1 in ferroptosis is context-dependent and cell-type-specific, a nuance that warrants further investigation in cardiomyocytes. Conversely, SAP30-binding protein (SAP30BP) was found to recruit HDAC1 to suppress the transcription of mitofusin-2 (MFN2), disrupting mitochondrial dynamics and exacerbating mitochondrial-associated ferroptosis in diabetic cardiomyopathy [4]. These observations underscore the complexity of HDAC1 signaling in the regulation of ferroptosis and highlight the need for cell-type-specific targeting strategies.

The therapeutic potential of HDAC1 inhibition extends beyond the Nrf2 pathway. A recent study identified the benzimidazole derivative as a selective HDAC1 inhibitor that induces ferroptosis by increasing the acetylation of Y-box binding protein 1 (YB-1) and suppressing Nrf2/HO-1 signaling in cancer cells [5]. While this appears contradictory to the cardioprotective effects described by Li et al. [1], it likely reflects tissue-specific differences, which is an important consideration for clinical translation. In the cardiovascular context, tanshinone IIA was identified as a high-affinity HDAC1 inhibitor that reduces myocardial ischemia-reperfusion injury by activating the Nrf2-xCT/GPX4/HO-1 axis, further validating HDAC1 as a druggable target for suppressing ferroptosis in the heart [6]. Notably, HDAC1 has also been implicated in regulating ferroptosis through non-Nrf2 mechanisms. Weighted gene co-expression network analysis (WGCNA) identified HDAC1 as a potential transcriptional regulator of arachidonate 15-lipoxygenase (ALOX15), a key mediator of ferroptosis [7].

Beyond ferroptosis, HDAC1 inhibitors have demonstrated multifaceted cardioprotective effects. Yixinshu capsules were shown to attenuate cardiac hypertrophy through the retinoblastoma protein (RB)/HDAC1/GATA-binding protein 4 (GATA4) pathway, although ferroptosis was not examined in that study [8]. Vericiguat, a soluble guanylate cyclase stimulator, reduces HDAC1 expression and exerts antihypertrophic effects, suggesting that its benefits may involve suggesting ferroptosis [9]. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, inhibits HDAC1 to restore nuclear respiratory factor 1 (NRF1)-mediated mitochondrial biogenesis and mitophagy, thereby improving cardiac hypertrophy [10]. Inhibition of HDAC1/2 has also been shown to suppress autophagy, a process closely linked to ferroptosis [11]. It is noteworthy that ferroptosis can be triggered by environmental stressors such as Particulate matter with an aerodynamic diameter of ≤2.5 μm (PM2.5) through ferritinophagy-mitophagy crosstalk, leading to cardiac hypertrophy [12]. S-nitrosylation of inhibitor of nuclear factor kappa-B kinase subunit gamma (IKKγ) promotes p65/HDAC1 interaction to activate cardiomyocyte proliferation, suggesting that HDAC1 modulates multiple cell fate decisions beyond death pathways [13].

Several outstanding questions remain. First, the precise molecular interaction between HDAC1 and Nrf2,

Table 1. Summary of key studies linking HDAC1, ferroptosis, and cardiac hypertrophy.

Thematic category	Core mechanism	Direct relevance to the letter
Core Support for HDAC1-Nrf2-Ferroptosis Axis	Identifies HDAC1 as a hub gene in HF with ferroptosis features [2]; Tanshinone IIA inhibit HDAC1 to relieve Nrf2 repression and activate xCT/GPX4/HO-1, suppressing cardiac ferroptosis [6].	Directly validates the central mechanism proposed by Li et al. [1] in a cardiac I/R model; provides clinical-transcriptomic and pharmacological evidence for HDAC1 targeting.
Context-Dependent and Cell-Type-Specific Roles of HDAC1 in Ferroptosis	HDAC1 acts as coactivator to suppress endothelial ferroptosis via SLC7A11 [3]; SAP30BP recruits HDAC1 to suppress MFN2, promoting cardiomyocyte ferroptosis [4]; HDAC1 inhibitor induces ferroptosis in cancer via YB-1/Nrf2 [5]; HDAC1 was predicted as a potential regulator of ALOX15 [7].	Highlights the cell-type and tissue-specific nature of HDAC1 function. This nuance is critical for safe clinical translation and is a key issue.
Pleiotropic Antihypertrophic Effects of HDAC1 Inhibition	RB/HDAC1/GATA4 [8]; Vericiguat reduces HDAC1 [9]; EGCG inhibits HDAC1-NRF1 to restore mitophagy [10]; HDAC1/2 suppress autophagy [11]; HDAC1 interacts with p65 to regulate proliferation [13].	Demonstrates that HDAC1 inhibitors improve hypertrophy through multiple converging pathways. Ferroptosis may be part of this network, strengthening the therapeutic rationale.
Key Ferroptosis-Hypertrophy Pathways That May Intersect with HDAC1	PM2.5 triggers ferritinophagy-mitophagy crosstalk and ferroptosis [12]; SIRT1 activates GPX4/HO-1 [14]; ACSL4 links ferroptosis to pyroptosis [15]; SLC7A11/xCT prevents Ang II induced ferroptosis [16].	Defines the broader ferroptosis network in hypertrophy. HDAC1 has not been tested in these contexts, making it a priority area for future mechanistic investigations.
Unresolved Mechanistic Gaps	Interaction between HDAC1 and Nrf2; interplay with SIRT1/ACSL4; regulation of SLC7A11 by HDAC1 in cardiomyocytes; dosing/cytotoxicity concerns.	Synthesizes the open questions raised in the correspondence, showing how the compiled references collectively point to these gaps rather than addressing them.

ACSL4, Acyl-CoA synthetase long-chain family member 4; ALOX15, Arachidonate 15-lipoxygenase; Ang II, Angiotensin II; EGCG, Epigallocatechin-3-gallate; GATA4, GATA-binding protein 4; GPX4, Glutathione peroxidase 4; HDAC1, Histone deacetylase 1; HO-1, Heme oxygenase-1; MFN2, Mitofusin-2; NRF1, Nuclear respiratory factor 1; Nrf2, Nuclear factor erythroid 2-related factor 2; PM2.5, Particulate matter with aerodynamic diameter ≤2.5 μm; RB, Retinoblastoma protein; SAP30BP, SAP30-binding protein; SIRT1, Sirtuin 1; SLC7A11, Solute carrier family 7 member 11; xCT, Cystine/glutamate antiporter subunit; YB-1, Y-box binding protein 1; I/R, Ischemia/reperfusion; HF, Heart failure.

whether direct binding or indirect regulation, requires validation through co-immunoprecipitation experiments. Second, the interplay between HDAC1 and other ferroptosis-regulating pathways remains unexplored in the context of cardiac hypertrophy. This includes sirtuin 1 (SIRT1) mediated GPX4/HO-1 activation [14] and acyl-CoA synthetase long-chain family member 4 (ACSL4)-dependent ferroptosis-pyroptosis crosstalk [15]. Third, the protective role of SLC7A11 against ferroptosis in Ang II-induced hypertrophy suggests that HDAC1 may also regulate this antiporter through additional mechanisms [16]. Table 1 (Ref. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16]) summarizes the relevant evidence.

In conclusion, the study by Li et al. [1] provides a foundation for targeting HDAC1 in cardiac hypertrophy. Future work should focus on delineating the cell-specific functions of HDAC1, optimizing dosing strategies to avoid the cytotoxicity observed at higher concentrations, and translating these findings into clinically feasible approaches for patients with heart failure.

Abbreviations

ACSL4, Acyl-CoA synthetase long-chain family member 4; ALOX15, Arachidonate 15-lipoxygenase; Ang II, Angiotensin II; BHLHE40, Basic helix-loop-helix family member e40; EGCG, Epigallocatechin-3-gallate; FTH1, Ferritin heavy chain 1; FPN, Ferroportin; GATA4, GATA-binding protein 4; GPX4, Glutathione peroxidase 4; HDAC, Histone deacetylase; HO-1, Heme oxygenase-1; IKKγ, Inhibitor of nuclear factor kappa-B kinase subunit gamma; MFN2, Mitofusin-2; NFAT2, Nuclear factor of activated T-cells, cytoplasmic 2; NRF1, Nuclear respiratory factor 1; Nrf2, Nuclear factor erythroid 2-related factor 2; Piezo1, Piezo-type mechanosensitive ion channel component 1; PM2.5, Particulate matter with aerodynamic diameter ≤2.5 μm; RB, Retinoblastoma protein; SAP30BP,

SAP30-binding protein; SIRT1, Sirtuin 1; SLC7A11, Solute carrier family 7 member 11; WGCNA, Weighted gene co-expression network analysis; xCT, Cystine/glutamate antiporter subunit; YB-1, Y-box binding protein 1.

Author Contributions

ZW: Conceptualization and design of the review framework; systematic literature search and screening; creating tables that summarize key concepts or evidence. CT: Critical appraisal of selected studies; interpretation of findings across studies. Both authors read and approved the final manuscript. Both authors contributed to editorial changes in the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used DeepSeek-V3 for the purpose of language polishing and grammar checking. After using this tool, the authors thoroughly reviewed and edited the output as necessary and take full responsibility for the entire content of the published work.

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