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Research Paper

Exploiting Mitochondria by Triggering a Faulty Unfolded Protein Response Leads to Effective Cardioprotection

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Abstract

This study investigates the role of Fundc1 in cardiac protection under high-altitude hypoxic conditions and elucidates its underlying molecular mechanisms. Using cardiomyocyte-specific *Fundc1* knockout (*Fundc1*^{CKO}) mice, we demonstrated that *Fundc1* deficiency exacerbates cardiac dysfunction under simulated high-altitude hypoxia, manifesting as impaired systolic and diastolic function. Mechanistically, we identified that Fundc1 regulates cardiac function through the mitochondrial unfolded protein response (mito-UPR) pathway. *Fundc1* deficiency led to significant downregulation of multiple mito-UPR-related factors, including ATF5, Chop, and PITRM1. Further investigation revealed that Fundc1 deficiency results in increased cardiomyocyte apoptosis, calcium dysregulation, reduced cell viability, and impaired mitochondrial function, characterized by decreased ATP production, reduced membrane potential, and increased ROS production. Notably, activation of mito-UPR with oligomycin significantly ameliorated these cardiac abnormalities in Fundc1-deficient mice. We identified ATF5 as a key downstream effector of Fundc1, as ATF5 overexpression effectively reversed cardiac dysfunction and restored mito-UPR-related gene expression in Fundc1-deficient hearts. Additionally, we discovered that Fundc1-mediated cardioprotection involves regulation of mitophagy, where its activation improved cardiac function and mitochondrial homeostasis in Fundc1-deficient mice. Our findings reveal a novel Fundc1-ATF5-mito-UPR axis in cardioprotection against high-altitude hypoxia and highlight the crucial role of mitophagy in this protective mechanism, providing new insights into potential therapeutic strategies for high-altitude heart disease.

Keywords: FUNDC1, ATF5, mito-UPR, mitochondria.

Introduction

High-altitude hypoxia-induced myocardial injury is a significant clinical problem, causing cardiac dysfunction and increased mortality [1-3]. The heart's high oxygen demand makes it vulnerable to hypoxia, triggering mitochondrial dysfunction, oxidative stress, calcium dysregulation, and apoptosis, ultimately impairing cardiac function [4-7]. While traditional therapies focus on symptom management and oxygen, research now emphasizes mitochondrial quality control pathways as crucial for cardiomyocyte survival under hypoxic stress.

The mitochondrial unfolded protein response (mito-UPR) is crucial for maintaining mitochondrial proteostasis under stress, including hypoxia [8-11]. This pathway, activated by mitochondrial protein misfolding, triggers transcriptional upregulation of chaperones, proteases, and other quality control factors via transcription factors like ATF5 [12-16]. The mito-UPR protects cardiomyocytes from stress, including ischemia-reperfusion and oxidative

damage, by enhancing mitochondrial function, reducing oxidative stress, and maintaining calcium homeostasis [17-20]. However, its regulation and role in cardiac protection during high-altitude hypoxia remain unclear.

Fundc1, a mitochondrial outer membrane protein, is a key regulator of mitochondrial quality control and adaptation to high-altitude hypoxia [21-25]. Initially identified as a mitophagy receptor, Fundc1 maintains mitochondrial function through selective autophagic degradation of damaged mitochondria [26-29]. Its activity, regulated by hypoxia and stress signals, is crucial for cardiomyocyte protection [30-34]. While Fundc1's role extends beyond mitophagy, its complete regulatory function in cardiac protection during high-altitude hypoxia requires further investigation.

The interplay between the mito-UPR and Fundc1-mediated protection is crucial for understanding cardiac adaptation to high-altitude hypoxia. These quality control mechanisms appear interconnected: mito-UPR activation influences mitochondrial dynamics regulated by Fundc1, while Fundc1-mediated mitophagy may impact mito-UPR activation. This bidirectional relationship, where Fundc1 may regulate mito-UPR components like ATF5 and mito-UPR activation influences FUNDC1-mediated mitophagy, offers potential therapeutic targets for high-altitude-induced cardiac injury.

Methods

Ethical statement

This study was performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals at China Academy of Chinese Medical Sciences. The animal study was approved by the Institutional Animal Care and Use Committee of China Academy of Chinese Medical Sciences (No. 241124).

Animal models

This study used cardiomyocyte-specific Fundc1 knockout ($Fundc1^{CKO}$) and control $Fundc1^{flox}$ mice [35], generated as previously described. Mice were housed under standard 12-hour light/dark cycles with free access to food and water. Following acclimatization, mice were exposed to simulated hypobaric hypoxia (5000m; 53.9 kPa, 11.2 kPa O_2, 24.9°C, 23.4% humidity) for 4 weeks in a chamber with a 10 m/s ascent/descent rate and 93.5 m^3/h ventilation, maintaining a near 12:12 light:dark cycle. Food and water were provided ad libitum, and chamber maintenance occurred daily between 8:00 and 9:00 AM [36].

Echocardiography

Cardiac function was assessed by echocardiography (high-resolution ultrasound) in isoflurane-anesthetized mice on a heated platform [37]. Left ventricular ejection fraction (LVEF), fractional shortening (LVFS), diastolic function (E/A, E'/E), and structural parameters (LVESD, LVEDD) were measured from parasternal long- and short-axis views. Data, averaged over three cardiac cycles, were analyzed by a blinded operator using specialized software [38].

Quantitative PCR (qPCR)

Cardiac tissue RNA was extracted using TRIzol, quality-checked with a NanoDrop, and reverse transcribed (1 μg input) using a high-capacity cDNA kit. qPCR (SYBR Green) was performed for mito-UPR-related genes with GAPDH as a control [38, 39]. Cycling conditions were 95°C for 10 minutes followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method [40].

Western blots

Proteins were extracted from heart tissues or cellular samples using RIPA buffer with protease and phosphatase inhibitors, quantified by Bradford assay, and 30 μg per sample were separated on 10% SDS-PAGE and transferred to PVDF membranes [41]. Membranes were blocked (5% milk/TBST), incubated overnight with primary antibodies, then with HRP-conjugated secondary antibodies. Detection used ECL, and bands were normalized to β-actin [42].

Cell viability assay

Cardiomyocyte viability under simulated high-altitude hypoxia was assessed by MTT assay. Cells (1×10^4/well) were treated, then incubated with MTT (10 μL, 5 mg/mL) for 4 hours [43]. Formazan crystals were dissolved in DMSO (100 μL), and absorbance measured at 570 nm. Viability was expressed as a percentage of the control [44].

Apoptosis assays

Apoptosis was assessed by caspase-3 activity (p-nitroaniline release measured at 405 nm) and TUNEL staining [45]. Fixed and permeabilized cardiomyocytes were TUNEL-stained, nuclei counterstained with DAPI, and TUNEL-positive cells counted (≥500 cells/sample) via fluorescence microscopy [46].

Calcium homeostasis

Intracellular calcium levels were measured using Fluo-4 AM (5 μM, 30 minutes, 37°C). After washing,

fluorescence intensity was measured microscopically, and images analyzed to quantify calcium levels under hypoxia [47].

JC-1 staining

Mitochondrial membrane potential was measured using JC-1 (5 μM, 20 minutes, 37°C) [48]. Following washes, red/green fluorescence ratios (aggregated/monomeric JC-1) were calculated from microscopy images to assess mitochondrial health [49].

Reactive Oxygen Species (ROS) levels

ROS levels were measured using DCFDA (10 μM, 30 minutes, 37°C). Post-wash, fluorescence was measured (Ex/Em: 485/535 nm) and expressed as relative fluorescence units, indicating oxidative stress [50].

ATP production

ATP levels were quantified using a luminescence-based assay [51]. Cardiomyocyte lysates were reacted with luciferase reagent, and luminescence, proportional to ATP concentration, was measured. ATP levels (nmol/mg protein) were calculated against a standard curve [52, 53].

Mitochondrial enzyme activity

Cytochrome c oxidase (COX) activity in isolated cardiac mitochondria was measured spectrophotometrically by monitoring reduced cytochrome c oxidation at 550 nm and expressed as units/mg protein [54, 55].

Statistical analysis

Data are presented as mean ± SD. Statistical analysis (GraphPad Prism) used Student's t-test or one-way ANOVA with Tukey's post-hoc test. Significance was set at $p < 0.05$.

Results

Fundc1 deficiency impacts cardiac function and the expression levels of the mito-UPR

To investigate Fundc1's role in hypoxia-induced myocardial injury, we compared cardiac function in *Fundc1*^{flox} (control) and *Fundc1*^{CKO} (knockout) mice under normoxia and simulated high-altitude hypoxia. *Fundc1*^{CKO} mice exhibited greater systolic (LVEF, LVFS), diastolic (E/A, E'/E), and structural (LVESD, LVEDD) impairments (Fig. 1A-F), demonstrating Fundc1's protective role against high-altitude hypoxia-induced cardiac damage.

Investigating Fundc1's cardioprotective mechanism, we examined the mito-UPR. qPCR (Fig. 1G-K) and Western blot (Fig. 1L-P) analyses revealed that Fundc1 deficiency dysregulates mito-UPR-related factors at both transcriptional and protein levels under simulated high-altitude hypoxia. Specifically, Fundc1 deficiency reduced expression of transcription factors (ATF5, Chop), proteases (Lonp1), chaperones (mtHsp70/mtDNAj), and enzymes (PITRM1), indicating Fundc1's protective role via mito-UPR modulation.

To understand Fundc1 deficiency's impact on cardiomyocyte survival, we assessed apoptosis and calcium homeostasis under simulated high-altitude hypoxia (Fig. 1Q-T). Fundc1 deficiency increased caspase-3 activity and TUNEL-positive cells, reduced cell viability, and elevated intracellular calcium. These findings, correlating with mito-UPR dysregulation, underscore Fundc1's cardioprotective role via the Fundc1/mito-UPR axis. By maintaining mito-UPR function, Fundc1 mitigates hypoxia-induced apoptosis and calcium dysregulation, preserving cardiac function.

Fundc1 protects heart function by activating mito-UPR

Having previously shown that Fundc1 deficiency downregulates mito-UPR factors *in vitro*, we activated the mito-UPR *in vivo* (Fig. 2A-F) to validate its role in Fundc1-mediated cardioprotection against Fundc1-deficiency-induced cardiac dysfunction.

Activating the mito-UPR with oligomycin (Figure 2) improved cardiac function in Fundc1-deficient mice under simulated high-altitude hypoxia, including improved systolic function (LVEF, LVFS), reduced ventricular dilation (LVEDD, LVESD), and improved diastolic function (E/A, E'/E).

These findings, consistent with FUNDC1's regulation of the mito-UPR, reinforce the importance of the Fundc1/mito-UPR axis in the cardiomyocyte response to high-altitude hypoxia. The observation that mito-UPR activation can compensate for Fundc1 deficiency's effects highlights the mito-UPR's role in Fundc1-mediated cardioprotection and offers a basis for new ischemic heart disease therapies.

Having established Fundc1's cardioprotective role via mito-UPR regulation, we investigated the effects of Fundc1 deficiency and mito-UPR activation on cardiomyocyte viability, apoptosis, and calcium homeostasis (Fig. 2G-J). Fundc1 deficiency increased susceptibility to reduced viability, apoptosis, calcium dyshomeostasis, and impaired energy metabolism under simulated high-altitude hypoxia. Mito-UPR activation with oligomycin mitigated these effects. These cellular findings explain the whole-heart functional changes and corroborate the

molecular-level mito-UPR expression alterations, further emphasizing the Fundc1-mito-UPR axis's importance in cardiomyocyte protection.

To understand Fundc1 deficiency's impact on mitochondrial function, we conducted experiments presented in Figure 2K-P. Fundc1 deficiency caused mitochondrial dysfunction under simulated high-altitude hypoxia, including decreased membrane potential, increased ROS, reduced enzyme activity, and decreased protein expression. Mito-UPR activation with oligomycin improved these abnormalities. These mitochondrial findings explain the observed cellular defects and corroborate the molecular changes in mito-UPR factors, highlighting the Fundc1/mito-UPR axis's importance in protecting cardiac function during high-altitude hypoxia.

Overexpression of ATF5 can improve cardiac function, restore mito-UPR activity, myocardial viability, mitochondrial structure and function

Having shown that Fundc1 deficiency downregulates mito-UPR factors, especially ATF5, we hypothesized ATF5 is a key downstream effector of Fundc1. To test this, we overexpressed ATF5 (Figure 3) to determine if it could rescue FUNDC1-deficiency-induced cardiac dysfunction.

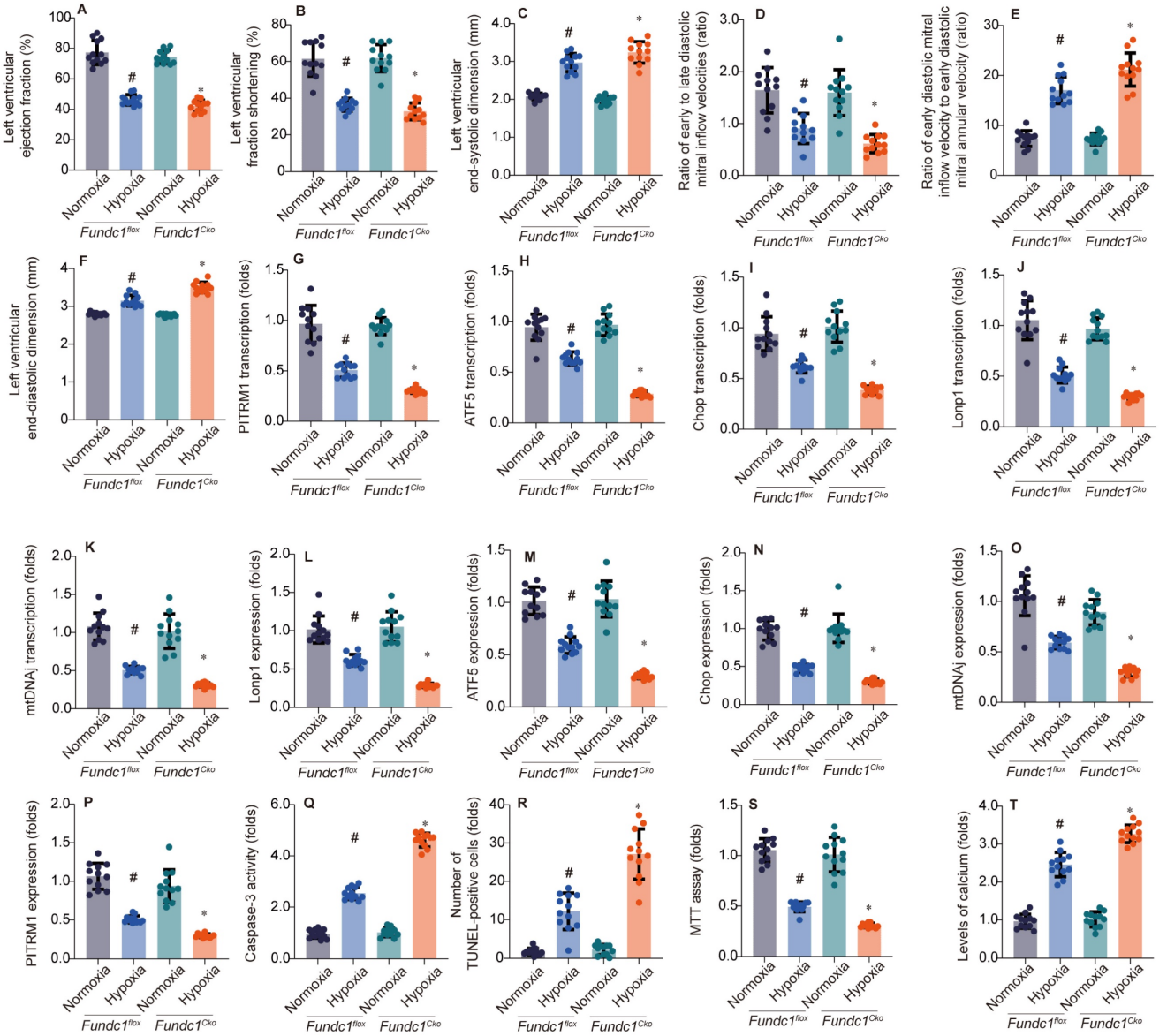

Figure 1. Fundc1 deficiency exacerbates hypoxia-induced cardiac dysfunction. Echocardiography showed FUNDC1 deficiency (Fundc1^{CKO}) worsened high-altitude hypoxia-induced cardiac dysfunction compared to controls (Fundc1^{flox}), affecting LVEF (A), LVFS (B), LVESD (C), E/A ratio (D), E/e' ratio (E), and LVEDD (F). (*$p < 0.05$ vs. normoxia; #$p < 0.05$ vs. Fundc1^{flox} under the same condition). Fundc1 deficiency alters the transcriptional response to hypoxia in the heart. Mitophagy and mitochondrial biogenesis marker mRNA expression (PITRM1 (G), ATF5 (H), Chop (I), Lonp1 (J), mtDNAJ (K)) were altered in FUNDC1-deficient (Fundc1^{CKO}) mice compared to controls (Fundc1^{flox}) under high-altitude hypoxia. (*$p < 0.05$ vs. normoxia; #$p < 0.05$ vs. Fundc1 under the same condition). Fundc1 deficiency alters the protein expression of mitophagy and mitochondrial biogenesis markers in response to hypoxia. Quantification (L-P) of Lonp1 (L), ATF5 (M), Chop (N), mtDNAJ (O), and PITRM1 (P) protein expression in Fundc1^{flox} and Fundc1^{CKO} mice under normoxic and high-altitude hypoxic conditions revealed alterations in FUNDC1-deficient mice. (*$p < 0.05$ vs. normoxia; #$p < 0.05$ vs.

Fundc1^{flox}). Fundc1 deficiency exacerbates hypoxia-induced cardiomyocyte apoptosis and dysfunction *in vitro*. FUNDC1 deficiency (Fundc1^{CKO}) increased cardiomyocyte apoptosis (caspase-3 activity (Q), TUNEL (R)) and reduced viability (MTT assay (S)) under high-altitude hypoxia compared to controls (Fundc1^{flox}). Intracellular calcium levels were also elevated in Fundc1^{CKO} cardiomyocytes (T). (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}).

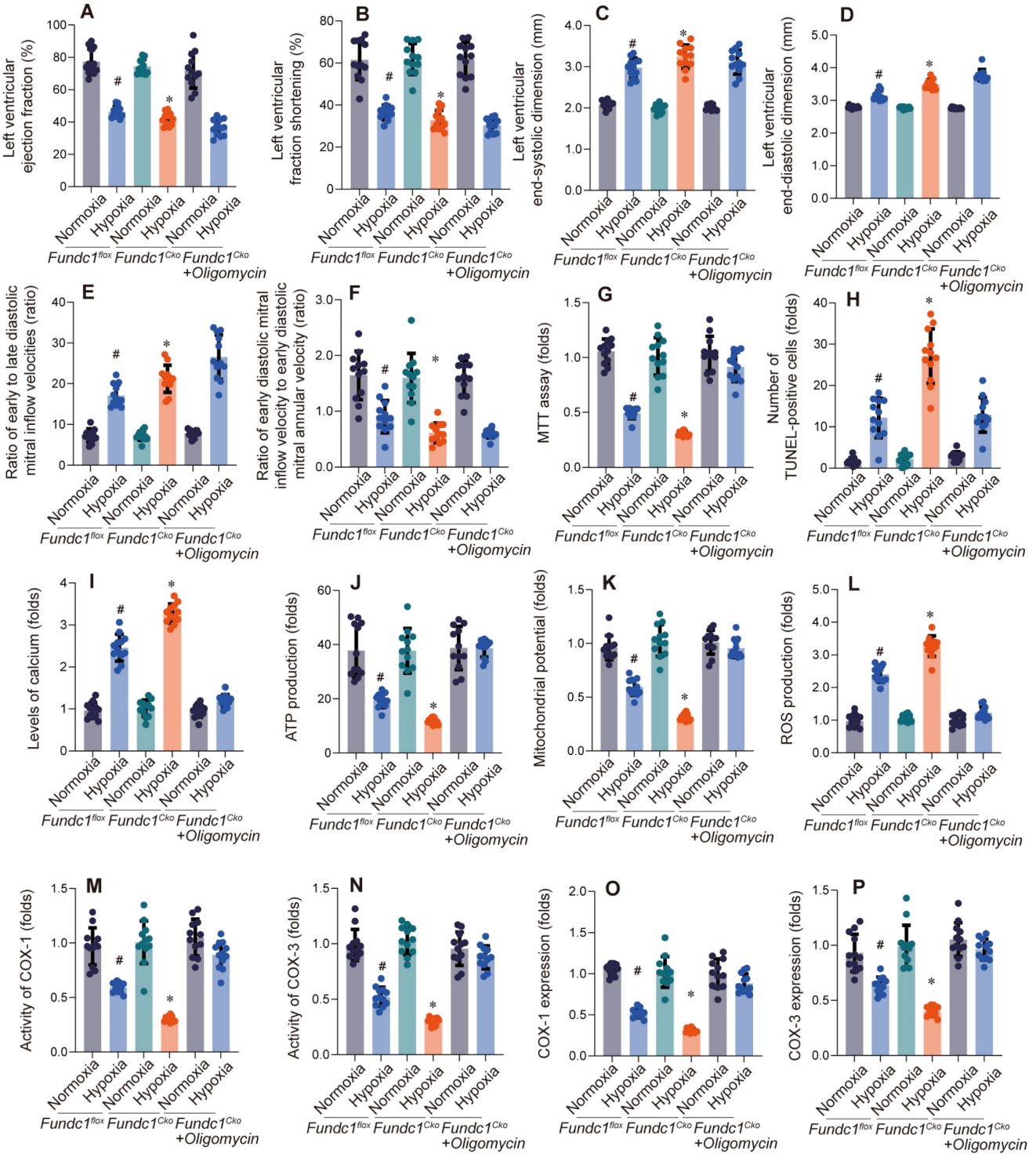

Figure 2. Oligomycin treatment rescues hypoxia-induced cardiac dysfunction in Fundc1^{CKO} mice. Echocardiography assessed cardiac function (LVEF (A), LVFS (B), LVESD (C), LVEDD (D), E/A ratio (E), E/e' ratio (F)) in Fundc1^{flox} and Fundc1^{CKO} mice under normoxic and high-altitude hypoxic conditions, with and without oligomycin. FUNDC1 deficiency worsened hypoxia-induced dysfunction. (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}). Oligomycin treatment rescues hypoxia-induced cardiomyocyte dysfunction and apoptosis *in vitro*. The effects of oligomycin treatment on cardiomyocyte viability (MTT assay (G)), apoptosis (TUNEL staining (H)), intracellular calcium (I), and ATP production (J) were assessed in Fundc1^{flox} and Fundc1^{CKO} cardiomyocytes under normoxic and high-altitude hypoxic conditions. FUNDC1 deficiency worsened hypoxia-induced changes in these parameters. (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}). Oligomycin treatment rescues hypoxia-induced mitochondrial dysfunction in Fundc1^{CKO} cardiomyocytes. Mitochondrial function was assessed in Fundc1^{flox} and Fundc1^{CKO} cardiomyocytes under normoxic and high-altitude hypoxic conditions with and without oligomycin. FUNDC1 deficiency impacted mitochondrial membrane potential (K), ROS production (L), COX activity (COX-1 (M), COX-3 (N)), and COX mRNA/protein expression (COX-1 (O), COX-3 (P)). (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}).

Overexpressing ATF5 (Fig. 3A-F) improved cardiac function in Fundc1-deficient mice, enhancing systolic function (LVEF, LVFS), diastolic function (E/A, e'/a'), and attenuating ventricular remodeling (LVEDD, LVESD). These findings, correlating with mito-UPR dysregulation, suggest ATF5 is a crucial downstream effector of FUNDC1, mediating cardioprotection against high-altitude hypoxia by activating the mito-UPR.

To explore ATF5's role in cardioprotection, we investigated its impact on mito-UPR gene expression in Fundc1-deficient mice (Fig. 3G-K). qPCR analysis revealed that ATF5 overexpression partially restored expression of mito-UPR-related genes, suggesting improved mitochondrial function. These findings support ATF5 as a key downstream effector of Fundc1, mediating cardioprotection against high-altitude hypoxia by activating mito-UPR-related genes.

To assess ATF5's cardioprotective effects, we examined its impact on Fundc1-deficient cardiomyocytes under simulated high-altitude hypoxia (Fig. 3L-O). ATF5 overexpression enhanced metabolic activity, reduced apoptosis, maintained calcium homeostasis, improved mitochondrial function, and increased ATP production.

The impact of Fundc1-mediated mitophagy on myocardial injury under high-altitude hypoxic conditions

Investigating Fundc1's cardioprotective mechanism via mito-UPR activation, we examined mitophagy's role (Fig. 4A-E). Fundc1 deficiency impaired systolic and diastolic function under simulated high-altitude hypoxia. Activating mitophagy improved cardiac function in Fundc1-deficient mice, while inhibiting it worsened dysfunction, confirming mitophagy's importance in Fundc1-mediated cardioprotection. Fundc1's benefits extended to preventing ventricular remodeling and preserving myocardial strain. These findings suggest Fundc1 promotes mitophagy to maintain mitochondrial quality and function, protecting the heart during high-altitude hypoxia.

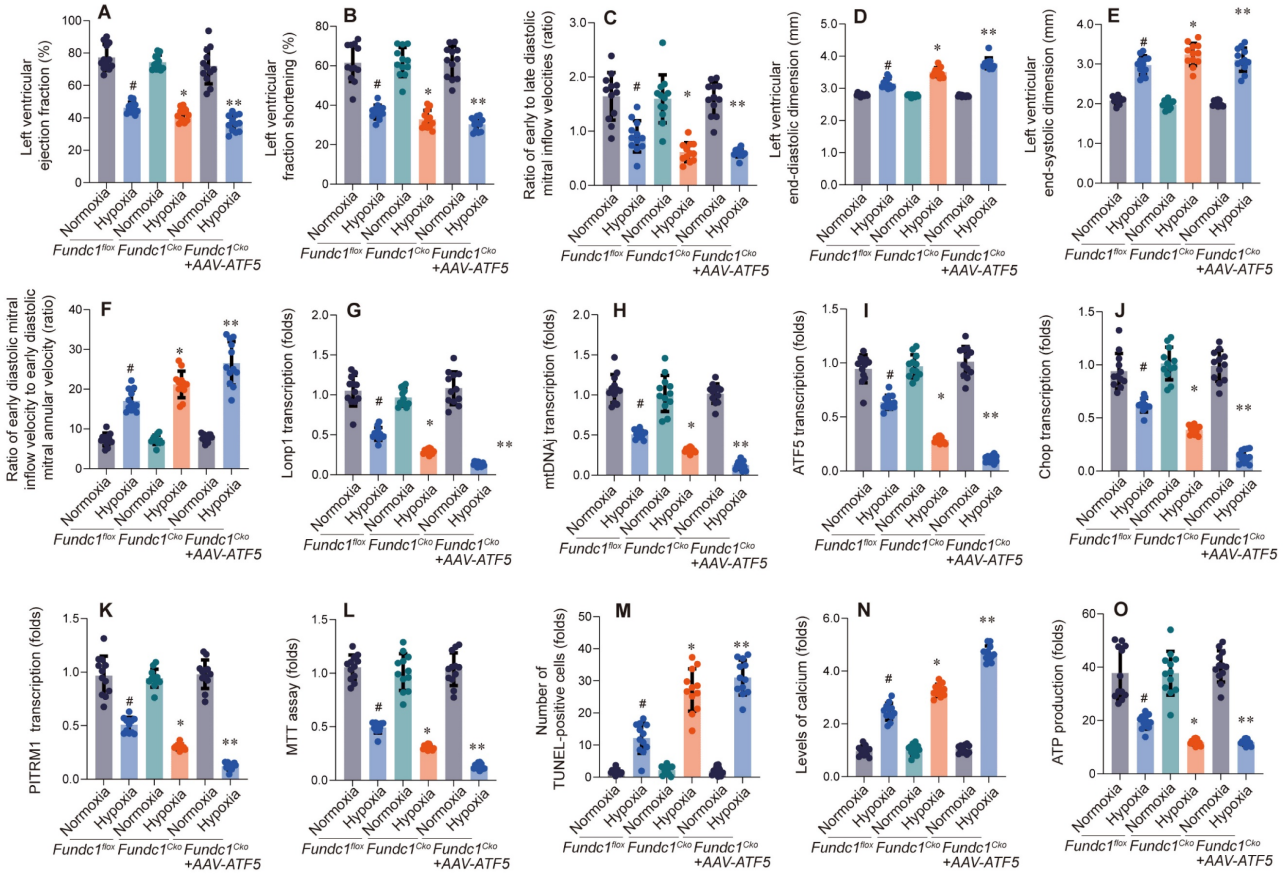

Figure 3. ATF5 overexpression rescues hypoxia-induced cardiac dysfunction in Fundc1^{CKO} mice. AAV-mediated ATF5 overexpression improved cardiac function in Fundc1^{CKO} mice under high-altitude hypoxia, as measured by LVEF (A), LVFS (B), E/A ratio (C), LVEDD (D), LVESD (E), and E/e' ratio (F). (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}; **p < 0.05 vs. Fundc1^{CKO} hypoxia). ATF5 overexpression rescues the altered transcriptional response to hypoxia in Fundc1^{CKO} hearts. AAV-ATF5 overexpression modulated mitophagy and mitochondrial biogenesis marker mRNA expression (Lonp1 (G), mtDNAJ (H), ATF5 (I), Chop (J), PITRM1 (K)) in Fundc1^{CKO} mice under high-altitude hypoxia. (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}; **p < 0.05 vs. Fundc1^{CKO} hypoxia). ATF5 overexpression rescues hypoxia-induced cardiomyocyte dysfunction and apoptosis *in vitro*. AAV-ATF5 overexpression improved cell viability (MTT assay (L)), reduced apoptosis (TUNEL staining (M)), decreased intracellular calcium levels (N), and increased ATP production (O) in Fundc1^{CKO} cardiomyocytes under high-altitude hypoxia. (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}; **p < 0.05 vs. Fundc1^{CKO} hypoxia).

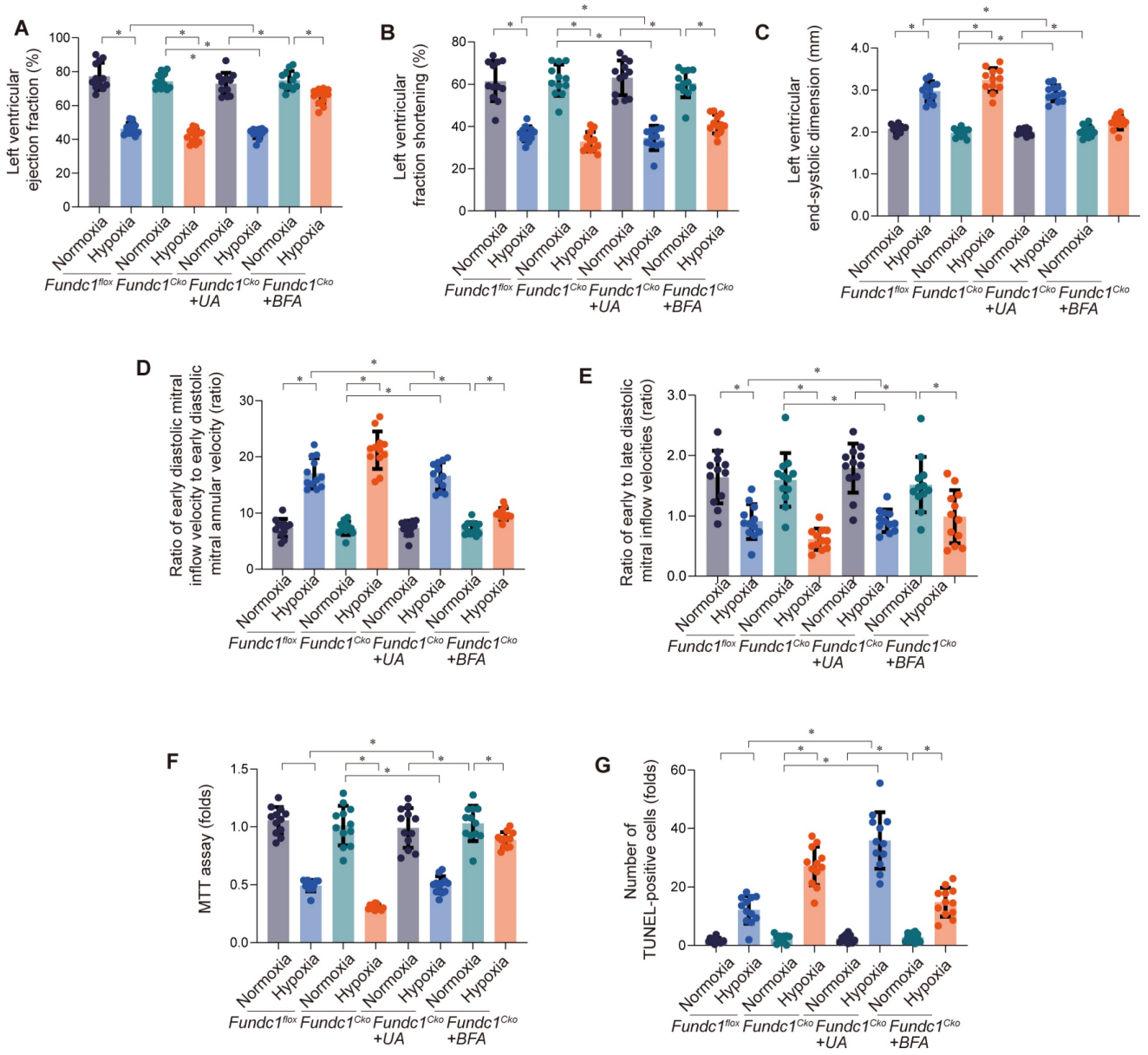

Figure 4. Inhibition of mitophagy rescues hypoxia-induced cardiac dysfunction in Fundc1^{CKO} mice. Mitophagy inhibition worsened cardiac function in Fundc1^{flox} and Fundc1^{CKO} mice under high-altitude hypoxia, as measured by LVEF (A), LVFS (B), LVESD (C), E/e' ratio (D), and E/A ratio (E). (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}). Inhibition of mitophagy rescues hypoxia-induced cardiomyocyte dysfunction and apoptosis *in vitro*. Mitophagy inhibition reduced cell viability (MTT assay (F)) and increased apoptosis (TUNEL staining (G)) in Fundc1^{flox} and Fundc1^{CKO} cardiomyocytes under high-altitude hypoxia. (*p < 0.05 vs. normoxia; #p < 0.05 vs. Fundc1^{flox}).

Having observed Fundc1-mediated mitophagy's impact on cardiac function (Fig. 4A-E), we investigated its effect on cardiomyocyte viability and apoptosis (Fig. 4F-G). Fundc1 deficiency reduced viability and increased apoptosis under simulated high-altitude hypoxia. Activating mitophagy rescued these effects in Fundc1-deficient cells, while inhibiting mitophagy worsened them, confirming its role in cardiomyocyte protection. These findings demonstrate Fundc1's direct protective effect on cardiomyocyte survival, extending beyond global cardiac function.

These findings demonstrate Fundc1's critical role in preserving mitochondrial respiratory function through both mitophagy and metabolic modulation, protecting against energy depletion and oxidative stress. This supports developing cardioprotective strategies targeting Fundc1 and mitophagy.

Discussion

This study reveals Fundc1's cardioprotective role during simulated high-altitude hypoxia. Fundc1-deficient mice exhibited exacerbated hypoxia-induced cardiac dysfunction, including impaired systolic and diastolic function and structural alterations, compared to controls [56]. This highlights Fundc1's importance in maintaining cardiac performance via mitochondrial quality control [57].

Furthermore, Fundc1 deficiency dysregulated mito-UPR factors, indicating Fundc1's role in modulating this protective response. Activating the mito-UPR partially rescued the dysfunction, suggesting the Fundc1/mito-UPR axis as a promising therapeutic target for high-altitude hypoxia-induced cardiac damage [58].

Furthermore, this study demonstrates Fundc1 deficiency leads to mitochondrial dysfunction, characterized by decreased ATP, increased ROS, and impaired respiratory chain activity. These findings highlight Fundc1-mediated mitophagy's role in mitochondrial quality control and cardiomyocyte survival [59], suggesting therapeutic potential for ischemic heart disease.

While this study advances understanding of Fundc1's cardioprotective role, limitations remain. The precise mechanisms of Fundc1's modulation of mito-UPR and mitophagy, and the broader implications of manipulating Fundc1's downstream effectors beyond ATF5, require further investigation [60, 61]. Future studies should explore these pathways and their potential synergy with other cardioprotective mechanisms.

In conclusion, this research highlights Fundc1's critical role in protecting the heart during high-altitude hypoxia, suggesting the Fundc1/mito-UPR axis as a promising therapeutic target for managing cardiac dysfunction.

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Competing Interests

The authors have declared that no competing interest exists.

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