Irisin activates Opa1-induced mitophagy to protect cardiomyocytes against apoptosis following myocardial infarction

Ting Xin¹², Chengzhi Lu²

¹The First Center Clinic College of Tianjin Medical University, Tianjin First Center Hospital, Tianjin, China
²Department of Cardiology, Tianjin First Center Hospital, Tianjin, China

Correspondence to: Chengzhi Lu; email: lucz8@126.com

Keywords: Opa1, irisin, myocardial infarction, mitophagy, mitochondria

INTRODUCTION

Myocardial infarction is characterized by sudden ischemia and cardiomyocyte death. Mitochondria have critical roles in regulating cardiomyocyte viability and can sustain damage under ischemic conditions. Mitophagy is a mechanism by which damaged mitochondria are removed by autophagy to maintain mitochondrial structure and function. We investigated the role of the dynamin-like GTPase optic atrophy 1 (Opa1) in mitophagy following myocardial infarction. Opa1 expression was downregulated in infarcted hearts in vivo and in hypoxia-treated cardiomyocytes in vitro. We found that Opa1 overexpression protected cardiomyocytes against hypoxia-induced damage and enhanced cell viability by inducing mitophagy. Opa1-induced mitophagy was activated by treatment with irisin, which protected cardiomyocytes from further damage following myocardial infarction. Opa1 knockdown abolished the cardioprotective effects of irisin resulting in an enhanced inflammatory response, increased oxidative stress, and mitochondrial dysfunction in cardiomyocytes. Our data indicate that Opa1 plays an important role in maintaining cardiomyocyte viability and mitochondrial function following myocardial infarction by inducing mitophagy. Irisin can activate Opa1-induced mitophagy and protect against cardiomyocyte injury following myocardial infarction.

Mitophagy is a mechanism by which damaged mitochondria are removed by autophagy to maintain mitochondrial structure and function. Mitophagy can block the release of ROS release from mitochondria and prevent apoptosis following mitochondrial damage in a lysosome-dependent process [10, 11]. Optic atrophy 1 (Opa1) is a dynamin-like GTPase that regulates fusion of the mitochondrial inner membrane [12]. Opa1 has been shown to regulate mitophagy through fusion-dependent and -independent mechanisms [13]. Interestingly, Opa1 has been shown to have cardioprotective effects [14]. Increased Opa1 expression was shown to reduce oxidative stress in cardiomyocytes in hypoxia-reperfusion injury through Ca²⁺/calmodulin-dependent protein kinase II (CaMKII signaling) [15]. Additionally, Opa1 upregulation reduced myocardial ischemia through activation of the Brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B (TrkB) pathway [16]. Reduced Opa1 expression...
inhibited mitophagy resulting in myocardial ischemia-reperfusion injury [17]. Finally, inhibition of mitophagy through PTEN-dependent upregulation of Opal protected cardiomyocytes against lipopolysaccharide (LPS)-mediated inflammation in a model of septic cardiomyopathy [18–20]. Thus, Opal may play a role in protecting cardiomyocytes from damage following myocardial infarction by regulating mitophagy [21, 22].

Mitophagy is important for regulating mitochondrial energy metabolism, oxidative stress, and apoptosis [23, 24]. Here, we investigated whether Opal promotes mitophagy to protect cardiomyocytes following myocardial infarction. Additionally, we explored whether irisin, a drug that has been shown to regulate mitochondrial function and suppress septic cardiomyopathy, could regulate Opal-induced mitophagy following myocardial infarction [25–28].

RESULTS

Opal is downregulated in the infarcted heart and in hypoxia-treated cardiomyocytes

We previously established an in vivo model of myocardial infarction [29, 30]. Using that model, we analyzed Opal expression in infarcted hearts compared to controls using quantitative real-time PCR and western blotting. Opal expression was lower in infarcted hearts compared to controls (sham) indicating Opal expression is downregulated following myocardial infarction (Figure 1A–1D). A reduction in Opal expression was also observed by immunofluorescence.

We also established an in vitro model of myocardial infarction in which cardiomyocytes were subjected to hypoxic conditions. Opal expression was reduced in cardiomyocytes cultured under hypoxic conditions for 48 hours compared to controls (Figure 1E, 1F), which is consistent with those of a previous findings [31]. Overexpression of Opal increased the viability hypoxia-treated cardiomyocytes as compared to untransfected controls (Figure 1G). Correspondingly, Opal overexpression in reduced the incidence of apoptosis among hypoxia-treated cardiomyocytes (Figure 1H–1I). These data suggest that Opal is important for protecting cardiomyocytes against hypoxia-induced damage.

Opal mediates mitophagy in the infarcted heart

Previous studies demonstrated that Opal can promote mitophagy [32, 33]. We therefore investigated the effect of hypoxia on mitophagy in cardiomyocytes by flow cytometry using the fluorescent reporter mt-Keima. We observed a reduction in mitophagy in hypoxia-treated cardiomyocytes compared to controls (Figure 2A, 2B). Interestingly, Opal overexpression resulted in an increase in mitophagy in hypoxia-treated cardiomyocytes, suggesting it may induce mitophagy in the infarcted heart [34, 35].

We previously demonstrated that irisin modulated mitochondrial function in a model of septic cardiomyopathy. We therefore hypothesized that irisin could modulate Opal-induced mitophagy in hypoxia-treated cardiomyocytes following myocardial infarction. Interestingly, we observed a decrease in the levels of various mitophagy-associated proteins under hypoxic conditions by western blotting. This effect was reversed by treatment with irisin, suggesting that irisin can activate Opal-induced mitophagy in cardiomyocytes under hypoxic stress (Figure 2C–2F).

Irisin activates Opal-induced mitophagy and restores mitochondrial energy metabolism

To investigate the mechanisms underlying the protective effects of Opal-induced mitophagy, we evaluated the alterations in mitochondrial function [36]. A reduction in the levels of mitochondria-derived ATP was observed in hypoxia-treated cardiomyocytes. Treatment with irisin resulted in an increase in ATP levels in hypoxia-treated cardiomyocytes compared to controls (Figure 3A) [37, 38]. The increase in ATP was inhibited by knockdown of Opal by siRNA (si-Opa1) (Figure 3A). We also observed downregulation of the levels of the mitochondrial respiratory complex in response to hypoxia, which was reversed by treatment with irisin (Figure 3B–3D). Knockdown of Opal by siRNA abolished the irisin-mediated protective effects on the mitochondrial respiratory complex (Figure 3B–3D). These results indicate that irisin exerts cardioprotective effects by activating Opal-induced mitophagy.

Opal-induced mitophagy maintains mitochondrial function and reduces oxidative stress

We further analyzed the protective effects of irisin and Opal-induced mitophagy following myocardial infarction [39, 40]. An increase in ROS in mitochondria was observed in hypoxia-treated cardiomyocytes (Figure 4A, 4B). Irisin reduced the levels of ROS whereas Opal knockdown by siRNA suppressed the antioxidative effects of irisin in hypoxia-treated cardiomyocytes (Figure 4A, 4B). Additionally, we found that the levels of components of the antioxidative system including glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GPX), were reduced under conditions of hypoxic stress (Figure 4C–4E). Interestingly, irisin promoted Opal-induced mitophagy and increased the levels of GSH, SOD, and
GPX (Figure 4C–4E). Thus, irisin promotes Opa1-induced mitophagy, which reduces oxidative stress.

We also found that the mitochondrial membrane potential, a marker of mitochondrial function, was disrupted by hypoxic stress (Figure 4F, 4G) [41, 42]. Irisin treatment restored the mitochondrial membrane potential in hypoxia-treated cardiomyocytes whereas Opa1 knockdown disrupted the mitochondrial membrane potential in irisin-treated cardiomyocytes (Figure 4F, 4G). These data indicate Opa1-induced mitophagy is important for maintaining mitochondrial function and reducing oxidative stress in cardiomyocytes.

**Opa1-induced mitophagy inhibits apoptosis**

We investigated whether Opa1-induced mitophagy could protect cardiomyocytes against hypoxia-induced apoptosis [43]. Caspase-3 activity increased in hypoxia-treated cardiomyocytes, which was indicative of activation of apoptotic cell death (Figure 5A) [44]. Treatment of hypoxia-treated cardiomyocytes with irisin inhibited caspase-3 activation. Finally, knockdown of Opa1 enhanced caspase-3 activation in irisin-treated cardiomyocytes (Figure 5A). These data indicate that the antiapoptotic effects of irisin are mediated by Opa1-induced mitophagy.

**Figure 1. Opa1 is downregulated in the infarcted heart and in hypoxia-treated cardiomyocytes.** (A–D) Quantitative real-time PCR and western blot analysis of Opa1 expression. (E, F) Analysis of Opa1 expression in cardiomyocytes in vitro by immunofluorescence. (G) MTT assays of cardiomyocyte viability. (H, I) Analysis of cardiomyocyte apoptosis by PI staining. *P < 0.05 vs. the control group; #P < 0.05 vs. the hypoxia + ctrl-OE group.
Figure 2. Irisin activates Opa1-induced mitophagy. (A, B) Flow cytometry analysis of mitophagy using the fluorescent probe mt-Keima. (C–F) Analysis of the expression of mitophagy-associated proteins by western blotting. *P < 0.05 vs. the control group; #P < 0.05 vs. the hypoxia + irisin group.

Figure 3. Irisin activates Opa1-induced mitophagy to restore mitochondrial energy metabolism. (A) Measurement of ATP production by ELISA. (B–D) Measurement of mitochondrial respiratory complex activity by ELISA. *P < 0.05 vs. the control group; #P < 0.05 vs. the hypoxia + irisin group.
The mitochondrial apoptotic pathway is characterized by cytochrome C (cyt-c) translocation to the cytoplasm. We observed an increase in cytoplasmic cyt-c levels by western blotting in hypoxia-treated cardiomyocytes (Figure 5B, 5C). Irisin treatment resulted in a decrease in the levels of cytoplasmic cyt-c in an Opa1-dependent manner (Figure 5B, 5C). The mitochondrial apoptotic pathway is also characterized by upregulation of caspase-9 and Bax [45]. We observed upregulation of both caspase-9 and Bax in hypoxia-treated cardiomyocytes by immunofluorescence (Figure 5D–5F). Treatment with irisin resulted in downregulation of caspase-9 and Bax in hypoxia-treated cardiomyocytes (Figure 5D–5F). Knockdown of Opa1 by siRNA resulted in an increase in caspase-9 and Bax levels in irisin- and hypoxia-treated cardiomyocytes (Figure 5D–5F). These data suggest that the anti-apoptotic effects of irisin require activation of Opa1-induced mitophagy in hypoxia-treated cardiomyocytes.

**Figure 4.** Opa1-induced mitophagy maintains mitochondrial function and reduces oxidative stress. (A, B) Analysis of ROS levels in cardiomyocytes. (C–E) ELISA assays to evaluate the levels of antioxidants. (F, G) Measurement of alterations in the mitochondrial membrane potential using a JC-1 probe. *P < 0.05 vs. the control group; #P < 0.05 vs. the hypoxia + irisin group.
DISCUSSION

Cardiomyocyte damage and death contributes to the pathogenesis of myocardial infarction [46, 47]. Myocardial infarction is caused by the sudden loss of blood supply to the heart and leads to cardiomyocyte death [48–50]. Death of cardiomyocytes results in activation of the inflammatory response [51, 52]. Additionally, the lack of blood flow and nutrients activates the transcription of pro-inflammatory factors that further enhance inflammation of the myocardium [53, 54]. Excessive inflammation can lead to the accumulation of pro-inflammatory cells such as white blood cells [55]. Although white blood cells are involved in repairing damage to the myocardium, they can also induce oxidative stress [56, 57]. The accumulation of these pro-inflammatory factors increases cardiomyocyte damage [58, 59].

Both mitochondria-dependent and -independent apoptotic pathways can lead to cardiomyocyte death [60, 61]. The mitochondria-dependent pathway is initiated in response to unrepaird mitochondrial damage. In contrast, the mitochondria-independent pathway is regulated by the endoplasmic reticulum [62, 63], lysosomes [64], and other factors. There are several

Figure 5. Opa1-induced mitophagy inhibits the mitochondrial apoptosis pathway. (A) Analysis of caspase-3 activity in cardiomyocytes by ELISA. (B, C) Western blot analysis of cyt-c levels in the cytoplasm and mitochondria. (D–F) Immunofluorescence analysis of Bax and caspase-9 expression in cardiomyocytes. *P < 0.05 vs. the control group; #P < 0.05 vs. the hypoxia + irisin group.
differences between the mitochondria-dependent and independent apoptosis pathways [65, 66]. The mitochondria-dependent pathway involves a reduction in mitochondrial membrane potential and activation of caspase-9 whereas the mitochondria-independent pathway is characterized by activation of caspase-3 and cellular membrane rupture [67]. We found that mitochondria-dependent apoptosis occurs during the progression of myocardial infarction. However, we could not exclude the possibility of mitochondria-independent apoptosis [68, 69]. We also found that the inflammatory response and oxidative stress were activated following myocardial infarction and could trigger cardiomyocyte death through the mitochondria-dependent apoptosis pathway [70].

Several studies have explored approaches for blocking mitochondria-dependent apoptosis in cardiomyocytes [71]. Mitophagy is a protective mechanism that involves the selective removal of dysfunctional mitochondria thereby allowing cellular repair [72]. Several proteins that are important for autophagy also play a role in mitophagy [73]. However, there are some proteins that are only involved in mitophagy including FUNDC1, BNIP3, PARK2, and NIX [74]. These proteins may have roles in cardiovascular diseases including myocardial infarction.

We previously demonstrated that the inner mitochondrial membrane protein Opa1 has an important role in promoting mitophagy [75, 76]. Consistent with previous studies, we found that irisin could activate Opa1-induced mitophagy in cardiomyocytes [77, 78]. Irisin treatment was associated with an increase in Opa1 expression. However, we did not evaluate whether there are differences in the expression of the Opa1 isoforms (L-Opa1 and S-Opa1) [79, 80]. Interestingly, Opa1 knockdown suppressed mitophagy and abolished the cardioprotective effects of irisin, suggesting that the protective effects of irisin on cardiomyocytes following myocardial infarction are dependent upon Opa1-induced mitophagy [81, 82].

Collectively, our data indicate that Opa1 plays an important role in regulating cardiomyocyte viability following myocardial infarction by activating mitophagy. Irisin can activate Opa1-induced mitophagy in the infarcted heart and could have therapeutic efficacy in patients with acute myocardial injury.

MATERIALS AND METHODS

Cell culture and animal models

Primary cardiomyocytes were isolated from and a model of myocardial infarction established as described [83, 84]. Cells were cultured under hypoxic conditions for 48 hours to mimic myocardial infarction [24, 85]. Cardiomyocytes were cultured in Dulbecco’s Modified Eagle Medium (DMEM, Sigma, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (Sigma, St. Louis, MO, USA) in a humidified atmosphere of 5% CO2 at 37°C. Irisin treatment was performed as described previously [86, 87].

Immunofluorescence staining

Cells seeded in plates were fixed with 4% paraformaldehyde and then blocked and permeabilized in solution containing 3% BSA (Sigma Aldrich, St. Louis, MO, USA), 10% normal goat serum (Vector Laboratories, Burlingame, CA, USA), and 0.3% Triton X-100 (Sigma Aldrich, St. Louis, MO, USA). The cells were then incubated with the indicated primary antibodies (Cell Signaling Technology, Danvers, MA, USA; Abcam, Cambridge, MA, USA) [88, 89]. Following the incubation, the cells were washed and incubated with corresponding Alexa Fluor secondary antibodies (Life Technologies, Carlsbad, CA, USA) [90, 91]. Lipid droplets and nuclei were stained with Hoechst 33342 prior to imaging the cells by confocal microscopy [92].

ROS measurement

Intracellular ROS levels were measured in cells plated in 6-well dishes at an equal density. The cells were trypsinized, washed with phosphate-buffered saline (PBS) [93, 94], and then stained with 2 µmol/L chloromethyl-2,7-dichlorodihydrofluorescein diacetate (CM-H2-DCFDA) (Life Technologies, Carlsbad, CA, USA). Relative cell counts were determined using a FACSComp II Analyzer flow cytometer (BD Biosciences, San Jose, CA, USA). Data were analyzed using the FlowJo software (FlowJo, LLC, Ashland, OR, USA) [95].

Opa1 knockdown and overexpression

Opa1 knockdown was performed using siRNA as described [96–99]. Briefly, cardiomyocytes were cultured in 6-well plates (1 x 10^6 / well), 6 cm dishes (3 x 10^5 / dish), or petri dishes (3 x 10^5 / well) [100]. The siRNA dose was the following: 50 pmol / petri dish, 100 pmol / 6-well plates, 166 pmol / 6 cm dish, and 434 pmol / 10 cm dish. Cell transfection with siRNA was performed using the Lipofectamine RNAiMAX Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer’s instructions [101]. Knockdown efficiency was evaluated 36 hours after transfection by quantitative real-time PCR. Adenovirus overexpression assays were performed as described previously [102].
Western blotting

Cells were washed with PBS and lysed in cold lysis buffer containing a protease inhibitor cocktail as described [103, 104]. Cell lysates were centrifuged at 13,000 g at 4 °C for 40 min. The supernatants were collected and total protein quantified [105]. Equal quantities of total protein were separated by 10% SDS-PAGE and transferred to nitrocellulose membranes (Millipore, Bedford, MA, USA). The membranes were incubated with primary antibodies at 4°C for 15 hours [106]. Following the incubation, the membranes were incubated with the respective secondary antibodies at 25°C for 90 minutes. Proteins were visualized using the ECL substrate (Thermo Fisher Scientific, Waltham, MA, USA). GAPDH was used as a loading control [107, 108].

Quantitative real-time PCR

RNA from serum was extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer’s protocol [109, 110]. The mRNA was reverse transcribed into cDNA using the First Strand Synthesis Kit (Thermo Fisher Scientific, Waltham, MA, USA) [111]. Real-time PCR was performed using an ABI7900 Real-time PCR system (Applied Biosystems, Foster City, CA, USA) using the SYBR Green Master Mix Kit (Takara, Dalian, China) [112]. We normalize mRNA expression to that of GAPDH. Relative gene expression was calculated using the comparative Ct method [113].

Enzyme-linked immunosorbent assays

The levels of antioxidants such as GSH, SOD, and GPX were evaluated using enzyme-linked immunosorbent assay (ELISA) kits (Abcam, Cambridge, MA, USA) according to the manufacturer’s instructions [112, 114].

Statistical analysis

Quantitative real-time PCR and ELISAs data were analyzed using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA) [115]. The data are presented as the mean ± standard deviation. Differences between groups were analyzed using unpaired t-tests. *A P < 0.05 was considered statistically significant [116].

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Abukar Y, Ramchandra R, Hood SG, McKinley MJ, Booth LC, Yao ST, May CN. Increased cardiac sympathetic nerve activity in ovine heart failure is reduced by lesion of the area postrema, but not lamina terminalis. Basic Res Cardiol. 2018; 113:35. https://doi.org/10.1007/s00395-018-0695-9 PMID:30076468

2. Aluja D, Inserfe J, Penela P, Ramos P, Ribas C, Iñiguez MA, Mayor F Jr, Garcia-Dorado D. Calpains mediate isoproterenol-induced hypertrophy through modulation of GRK2. Basic Res Cardiol. 2019; 114:21. https://doi.org/10.1007/s00395-019-0730-5 PMID:30915659

3. Amanakis G, Kleinbongard P, Heusch G, Skyschally A. Attenuation of ST-segment elevation after ischemic conditioning maneuvers reflects cardioprotection online. Basic Res Cardiol. 2019; 114:22. https://doi.org/10.1007/s00395-019-0732-3 PMID:30937537

4. Audia JP, Yang XM, Crockett ES, Housley N, Haq EU, O’Donnell K, Cohen MV, Downey JM, Alvarez DF. Caspase-1 inhibition by VX-765 administered at reperfusion in P2Y12 receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. Basic Res Cardiol. 2018; 113:32. https://doi.org/10.1007/s00395-018-0692-z PMID:29992382

5. Ham SW, Jeon HY, Jin X, Kim EJ, Kim JK, Shin YJ, Lee Y, Kim SH, Lee SY, Seo S, Park MG, Kim HM, Nam DH, Kim H. TP53 gain-of-function mutation promotes inflammation in glioblastoma. Cell Death Differ. 2019; 26:409–25. https://doi.org/10.1038/s41418-018-0126-3 PMID:29786075

6. Hill SM, Wrobel L, Rubinsztein DC. Post-translational modifications of Beclin 1 provide multiple strategies for autophagy regulation. Cell Death Differ. 2019; 26:617–29. https://doi.org/10.1038/s41418-018-0254-9 PMID:30546075

7. Bacmeister L, Schwarzl M, Warnke S, Stoffers B, Blankenberg S, Westermann D, Lindner D. Inflammation and fibrosis in murine models of heart failure. Basic Res Cardiol. 2019; 114:19. https://doi.org/10.1007/s00395-019-0722-5 PMID:30887214

8. Basalay MV, Davidson SM, Gourine AV, Yellon DM. Neural mechanisms in remote ischemic conditioning in the heart and brain: mechanistic and translational aspects. Basic Res Cardiol. 2018; 113:25. https://doi.org/10.1007/s00395-018-0684-z PMID:29858664

9. Hockings C, Alsop AE, Fennell SC, Lee EF, Fairlie WD, Dewson G, Kluck RM. Mcl-1 and Bcl-x, sequestration of...
Bak confers differential resistance to BH3-only proteins. Cell Death Differ. 2018; 25:721–34. https://doi.org/10.1038/s41418-017-0010-6 PMID:29459767

10. Huang S, Li Y, Yuan X, Zhao M, Wang J, Li Y, Li Y, Lin H, Zhang Q, Wang W, Li D, Dong X, Li L, et al. The UbL-UBA Ubiquilin4 protein functions as a tumor suppressor in gastric cancer by p53-dependent and p53-independent regulation of p21. Cell Death Differ. 2019; 26:516–30. https://doi.org/10.1038/s41418-018-0141-4 PMID:29899380

11. Baker HE, Kiel AM, Luebbe ST, Simon BR, Earl CC, Regmi A, Roell WC, Mather KJ, Tune JD, Goodwill AG. Inhibition of sodium-glucose cotransporter-2 preserves cardiac function during regional myocardial ischemia independent of alterations in myocardial substrate utilization. Basic Res Cardiol. 2019; 114:25. https://doi.org/10.1007/s00395-019-0733-2 PMID:31004234

12. Beckendorf J, van den Hoogenhof MM, Backs J. Physiological and unappreciated roles of CaMKII in the heart. Basic Res Cardiol. 2018; 113:29. https://doi.org/10.1007/s00395-018-0688-8 PMID:29905892

13. Knupp J, Arvan P, Chang A. Increased mitochondrial respiration promotes survival from endoplasmic reticulum stress. Cell Death Differ. 2019; 26:487–501. https://doi.org/10.1038/s41418-018-0133-4 PMID:29795335

14. Betkhe HE, Hausenloy D, Andreadou I, Antonucci S, Boengler K, Davidson SM, Deshwal S, Devaux Y, Di Lisa F, Di Sante M, Efentakis P, Femminò S, Garcia-Dorado D, et al. Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection. Basic Res Cardiol. 2018; 113:39. https://doi.org/10.1007/s00395-018-0696-8 PMID:30120595

15. Luo H, Song S, Chen Y, Xu M, Sun L, Meng G, Zhang W. Inhibitor 1 of Protein Phosphatase 1 Regulates Ca²⁺/Calmodulin-Dependent Protein Kinase II to Alleviate Oxidative Stress in Hypoxia-Reoxygenation Injury of Cardiomyocytes. Oxid Med Cell Longev. 2019; 2019:2193019. https://doi.org/10.1155/2019/2193019 PMID:31885777

16. Wang Z, Wang SP, Shao Q, Li PF, Sun Y, Luo LZ, Yan XQ, Fan ZY, Hu J, Zhao J, Hang PZ, Du ZM. Brain-derived neurotrophic factor mimetic, 7,8-dihydroxyflavone, protects against myocardial ischemia by rebalancing optic atrophy 1 processing. Free Radic Biol Med. 2019; 145:187–97. https://doi.org/10.1016/j.freeradbiomed.2019.09.033 PMID:31574344

17. Guan L, Che Z, Meng X, Yu Y, Li M, Yu Z, Shi H, Yang D, Yu M. MCU Up-regulation contributes to myocardial ischemia-reperfusion Injury through calpain/OPA-1-mediated mitochondrial fusion/mitophagy Inhibition. J Cell Mol Med. 2019; 23:7830–43. https://doi.org/10.1111/jcmm.14662 PMID:31502361

18. Jain R, Mintern JD, Tan I, Dewson G, Strasser A, Gray DH. How do thymic epithelial cells die? Cell Death Differ. 2018; 25:1002–04. https://doi.org/10.1038/s41418-018-0093-8 PMID:29549302

19. Jilg A, Bechstein P, Saade A, Dick M, Li TX, Tosini G, Rami A, Zemmar A, Stehle JH. Melatonin modulates daytime-dependent synaptic plasticity and learning efficiency. J Pineal Res. 2019; 66:e12553. https://doi.org/10.1111/jpi.12553 PMID:30618149

20. Li J, Shi W, Zhang J, Ren L. To Explore the Protective Mechanism of PTEN-Induced Kinase 1 (PINK1)/Parkin Mitophagy-Mediated Extract of Periplaneta Americana on Lipopolysaccharide-Induced Cardiomyocyte Injury. Med Sci Monit. 2019; 25:1383–91. https://doi.org/10.12659/MSM.912980 PMID:30789157

21. Cao T, Fan S, Zheng D, Wang G, Yu Y, Chen R, Song LS, Fan GC, Zhang Z, Peng T. Increased calpain-1 in mitochondria induces dilated heart failure in mice: role of mitochondrial superoxide anion. Basic Res Cardiol. 2019; 114:17. https://doi.org/10.1007/s00395-019-0726-1 PMID:30874894

22. Jeelani R, Malir D, Chatzicharalampous C, Najeemuddin S, Morris RT, Abu-Soud HM. Melatonin prevents hypochlorous acid-mediated cyanocobalamin destruction and cyanogen chloride generation. J Pineal Res. 2018; 64:64. https://doi.org/10.1111/jpi.12463 PMID:29247550

23. Coverstone ED, Bach RG, Chen L, Bierut LJ, Li AY, Lenzini PA, O’Neill HC, Spertus JA, Sucharov CC, Stitzel JA, Schilling JD, Cresci S. A novel genetic marker of rheumatoid arthritis. J Pineal Res. 2019; 66:e12563. https://doi.org/10.1111/jpi.12560 PMID:30648758

24. Curley D, Lavin Plaza B, Shah AM, Botnar RM. Molecular imaging of cardiac remodelling after
myocardial infarction. Basic Res Cardiol. 2018; 113:10. https://doi.org/10.1007/s00395-018-0668-z
PMID: 29344827

26. Schoenfeld JD, Sibenaller ZA, Mapuskar KA, Bradley MD, Wagner BA, Buettner GR, Monga V, Milhem M, Spitz DR, Allen BG. Redox active metals and H2O2 mediate the increased efficacy of pharmacological ascorbate in combination with gemcitabine or radiation in pre-clinical sarcoma models. Redox Biol. 2018; 14:417–22. https://doi.org/10.1016/j.redox.2017.09.012
PMID: 29069637

27. Dassanayaka S, Brittian KR, Jurkovic A, Higgins LA, Audam TN, Long BW, Harrison LT, Militello G, Riggs DW, Chitre MG, Uchida S, Muthusamy S, Gumpert AM, Jones SP. E2F1 deletion attenuates infarct-induced ventricular remodeling without affecting O-GlcNAcylation. Basic Res Cardiol. 2019; 114:28. https://doi.org/10.1007/s00395-019-0737-v
PMID: 31152247

28. Serrato AJ, Romero-Puertas MC, Lázaro-Payo A, Sahrawy M. Regulation by S-nitrosylation of the Calvin-Benson cycle fructose-1,6-bisphosphatase in Pisum sativum. Redox Biol. 2018; 14:409–16. https://doi.org/10.1016/j.redox.2017.10.008
PMID: 29059554

29. Heusch G. Coronary microvascular obstruction: the new frontier in cardioprotection. Basic Res Cardiol. 2019; 114:45. https://doi.org/10.1007/s00395-019-0756-8
PMID: 31617010

30. Zhou L, Zhang H, Davies KJ, Forman HJ. Aging-related decline in the induction of Nrf2-regulated antioxidant genes in human bronchial epithelial cells. Redox Biol. 2018; 14:35–40. https://doi.org/10.1016/j.redox.2017.08.014
PMID: 28863281

31. Ciani E, Fontaine R, Maugars G, Mizrahi N, Mayer I, Levavi-Sivan B, Weltzien FA. Melatonin receptors in Atlantic salmon stimulate cAMP levels in heterologous cell lines and show season-dependent daily variations in pituitary expression levels. J Pineal Res. 2019; 67:e12590. https://doi.org/10.1111/jp1.12590 PMID: 31169933

32. Chen Y, Liu K, Shi Y, Shao C. The tango of ROS and p53 in tissue stem cells. Cell Death Differ. 2018; 25:639–41. https://doi.org/10.1038/s41418-018-0062-2
PMID: 29487352

33. Zhou YQ, Liu DQ, Chen SP, Sun J, Zhou XR, Rittner H, Mei W, Tian YK, Zhang HX, Chen F, Ye DW. Reactive oxygen species scavengers ameliorate mechanical allostynia in a rat model of cancer-induced bone pain. Redox Biol. 2018; 14:391–97. https://doi.org/10.1016/j.redox.2017.10.011
PMID: 29055283

34. Cecon E, Ivanova A, Luka M, Gbahou F, Friederic h A, Guillaume JL, Keller P, Knock K, Ahmad R, Delargrange P, Solimena M, Jockers R. Detection of recombinant and endogenous mouse melatonin receptors by monoclonal antibodies targeting the C-terminal domain. J Pineal Res. 2019; 66:e12540. https://doi.org/10.1111/jp1.12540 PMID:30475390

35. Chen YT, Yang CC, Shao PL, Huang CR, Yip HK. Melatonin-mediated downregulation of ZNF746 suppresses bladder tumorigenesis mainly through inhibiting the AKT-MMP-9 signaling pathway. J Pineal Res. 2019; 66:e12536. https://doi.org/10.1111/jp1.12536 PMID:30372570

36. Hofmann F. A concise discussion of the regulatory role of cGMP kinase I in cardiac physiology and pathology. Basic Res Cardiol. 2018; 113:31. https://doi.org/10.1007/s00395-018-0690-1
PMID: 29934662

37. Ba X, Boldogh I. 8-Oxoguanine DNA glycosylase 1: beyond repair of the oxidatively modified base lesions. Redox Biol. 2018; 14:669–78. https://doi.org/10.1016/j.redox.2017.11.008
PMID: 29175754

38. Brazão V, Colato RP, Santello FH, Vale GT, Gonzaga NA, Tirapelli CR, Prado JC Jr. Effects of melatonin on thymic proliferation and oxidative stress dysf Eight additional genes expressed in thymic stromal cells. Front Immunol. 2018; 9:1311. https://doi.org/10.3389/fimmu.2018.01311
PMID: 29781553

39. Honda T, He Q, Wang F, Redington AN. Acute and chronic remote ischemic conditioning attenuate septic cardiomyopathy, improve cardiac output, protect systemic organs, and improve mortality in a lipopolysaccharide-induced sepsis model. Basic Res Cardiol. 2019; 114:15. https://doi.org/10.1007/s00395-019-0724-3
PMID: 30838474

40. Chen H, Kankel MW, Su SC, Han SW, Ofengeim D. Exploring the genetics and non-cell autonomous mechanisms underlying ALS/FTLD. Cell Death Differ. 2018; 25:648–62. https://doi.org/10.1038/s41418-018-0060-4
PMID: 29459769

41. Hou L, Guo J, Xu F, Weng X, Yue W, Ge J. Cardiomyocyte dimethylarginine dimethylaminohydrolase1 attenuates left-ventricular remodeling after acute myocardial infarction: involvement in oxidative stress and apoptosis. Basic Res Cardiol. 2018; 113:28. https://doi.org/10.1007/s00395-018-0685-y
PMID: 29892894
42. Bellot GL, Dong X, Lahiri A, Sebastian SJ, Batinic-Haberle I, Pervaiz S, Puhaindran ME. MnSOD is implicated in accelerated wound healing upon Negative Pressure Wound Therapy (NPWT): A case in point for MnSOD mimetics as adjuvants for wound management. Redox Biol. 2019; 20:307–20. https://doi.org/10.1016/j.redox.2018.10.014 PMID:30390545

43. Jiang Q, Xiang B, Wang H, Huang K, Kong H, Hu S. Remote ischaemic preconditioning ameliorates sinus rhythm restoration rate through Cox maze radiofrequency procedure associated with inflammation reaction reduction. Basic Res Cardiol. 2019; 114:14. https://doi.org/10.1007/s00395-019-0723-4 PMID:30838448

44. Carè A, Bellenghi M, Matarrese P, Gabriele L, Salvioli S, Malorni W. Sex disparity in cancer: roles of microRNAs and related functional players. Cell Death Differ. 2018; 25:477–85. https://doi.org/10.1038/s41418-017-0051-x PMID:29352271

45. Biernacki M, Ambrożewicz E, Gegotek A, Toczek M, Bielawska K, Skrzypewska E. Redox system and phospholipid metabolism in the kidney of hypertensive rats after FAAH inhibitor UR8597 administration. Redox Biol. 2018; 15:41–50. https://doi.org/10.1016/j.redox.2017.11.022 PMID:29197803

46. Cabon L, Bertaux A, Brunelle-Navas MN, Nemazanyy I, Scourzic L, Delavallée L, Vela L, Baritaud M, Bouchet S, Lopez C, Quang Van V, Garbin K, Chateau D, et al. AIF loss deregulates hematopoiesis and reveals different adaptive metabolic responses in bone marrow cells and thymocytes. Cell Death Differ. 2018; 25:983–1001. https://doi.org/10.1038/s41418-017-0035-x PMID:29323266

47. Heppner DE, Hristova M, Ida T, Mijuskovic A, Dustin CM, Bogdándi V, Fukuto JM, Dick TP, Nagy P, Li J, Akaike T, van der Vliet A. Cysteine persulphenic acid (Cys-SSOH): A novel intermediate in thiol-based redox signaling? Redox Biol. 2018; 14:379–85. https://doi.org/10.1016/j.redox.2017.10.006 PMID:29054072

48. Kleinbongard P, Skyschally A, Gent S, Pesch M, Heusch G. STAT3 as a common signal of ischemic conditioning: a lesson on “rigor and reproducibility” in preclinical studies on cardioprotection. Basic Res Cardiol. 2017; 113:3. https://doi.org/10.1007/s00395-017-0660-z PMID:29159507

49. Bramasole L, Sinha A, Gurevich S, Radzinski M, Klein Y, Panat N, Gefen E, Rinaldi T, Jimenez-Morales D, Johnson J, Krogan NJ, Reis N, Reichmann D, et al. Proteasome lid bridges mitochondrial stress with Cdc53/Cullin1 NEDDylation status. Redox Biol. 2019; 20:533–43. https://doi.org/10.1016/j.redox.2018.11.010 PMID:30508698

50. Hatori Y, Inouye S, Akagi R, Seyama T. Local redox environment beneath biological membranes probed by palmitoylated-roGFP. Redox Biol. 2018; 14:679–85. https://doi.org/10.1016/j.redox.2017.11.015 PMID:29179107

51. Bittremieux M, La Rovere RM, Aki H, Martines C, Welkenhuyzen K, Dubron K, Baes M, Janssens A, Vandenberghhe P, Laurenti L, Rietdorf K, Morciano G, Pintor P, et al. Constitutive IP$_3$ signaling underlies the sensitivity of B-cell cancers to the Bcl-2/IP$_3$ receptor disruptor BIRD-2. Cell Death Differ. 2019; 26:531–47. https://doi.org/10.1038/s41418-018-0142-3 PMID:29899382

52. Shiri F, Pirhadi S, Rahmani A. Identification of new potential HIV-1 reverse transcriptase inhibitors by QSAR modeling and structure-based virtual screening. J Recept Signal Transduct Res. 2018; 38:37–47. https://doi.org/10.1080/10799893.2017.1414844 PMID:29254400

53. Capece D, D’Andrea D, Verzella D, Tornatore L, Begalli F, Bennett J, Zazzeroni F, Franzoso G. Turning an old GADDget into a troublemaker. Cell Death Differ. 2018; 25:642–44. https://doi.org/10.1038/s41418-018-0087-6 PMID:29511335

54. Chandra M, Escalante-Alcalde D, Bhuiyan MS, Orr AW, Kevil C, Morris AJ, Nam H, Dominic P, McCarthy KJ, Miriyala S, Panchatcharam M. Cardiac-specific inactivation of LPP3 in mice leads to myocardial dysfunction and heart failure. Redox Biol. 2018; 14:261–71. https://doi.org/10.1016/j.redox.2017.09.015 PMID:28982073

55. Chandrasekharan A, Varadarajan SN, Lekshmi A, Lupitha SS, Darvin P, Chandrasekhar L, Pillai PR, Santhoshkumar TR, Pillai MR. A high-throughput real-time in vitro assay using mitochondrial targeted roGFP for screening of drugs targeting mitochondria. Redox Biol. 2019; 20:379–89. https://doi.org/10.1016/j.redox.2018.10.013 PMID:30408753

56. Hou L, Wang K, Zhang C, Sun F, Che Y, Zhao X, Zhang D, Li H, Wang Q. Complement receptor 3 mediates NADPH oxidase activation and dopaminergic neurodegeneration through a Src-Erk-dependent pathway. Redox Biol. 2018; 14:250–60.
57. Saba Khan N, Verma R, Pradhan D, Nayek A, Bhuyan R, Kumar Sahu T, Kumar Jain A. Analysis of interleukin 23 and 7G10 interactions for computational design of lead antibodies against immune-mediated inflammatory diseases. J Recept Signal Transduct Res. 2018; 38:327–34. https://doi.org/10.1080/10799893.2018.1511729 PMID: 30481093

58. Chang HC, Kao CH, Chung SY, Chen WC, Aninda LP, Chen YH, Juan YA, Chen SL. Bhlhe40 differentially regulates the function and number of peroxisomes and mitochondria in myogenic cells. Redox Biol. 2019; 20:321–33. https://doi.org/10.1016/j.redox.2018.10.009 PMID: 30391825

59. Hao L, Sun Q, Zhong W, Zhang W, Sun X, Zhou Z. Mitochondria-targeted ubiquinone (MitoQ) enhances acetaldehyde clearance by reversing alcohol-induced posttranslational modification of aldehyde dehydrogenase 2: A molecular mechanism of protection against alcoholic liver disease. Redox Biol. 2018; 14:626–36. https://doi.org/10.1016/j.redox.2017.11.005 PMID: 29156373

60. Koentges C, Pepin ME, Műsse C, Pfeif K, Alvarez SV, Hoppe N, Hoffmann MM, Odening KE, Sossalla S, Zirlik A, Hein L, Bode C, Wende AR, Bugger H. Gene expression analysis to identify mechanisms underlying heart failure susceptibility in mice and humans. Basic Res Cardiol. 2017; 113:8. https://doi.org/10.1007/s00395-017-0666-6 PMID: 29288409

61. Ruiz-Hernández A, Romero-Nava R, Huang F, Hong E, Villafañ a S. Altered function and expression of the orphan GPR135 at the cardiovascular level in diabetic Wistar rats. J Recept Signal Transduct Res. 2018; 38:484–91. https://doi.org/10.1080/10799893.2019.1597116 PMID: 31038027

62. Bellomo C, Caja L, Fabregat I, Mikulits W, Kardassi D, Heldin CH, Moustakas A. Snail mediates crosstalk between TGFβ and LXRα in hepatocellular carcinoma. Cell Death Differ. 2018; 25:885–903. https://doi.org/10.1038/s41418-017-0021-3 PMID: 29230000

63. Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer’s disease. Redox Biol. 2018; 14:450–64. https://doi.org/10.1016/j.redox.2017.10.014 PMID: 29080524

64. Guidarelli A, Fiorani M, Cerioni L, Cantoni O. Calcium signals between the ryanodine receptor- and mitochondria critically regulate the effects of arsenite on mitochondrial superoxide formation and on the ensuing survival vs apoptotic signaling. Redox Biol. 2019; 20:285–95. https://doi.org/10.1016/j.redox.2018.10.015 PMID: 30388683

65. Cremonini E, Wang Z, Bettai eb A, Adamo AM, Daveri E, Mills DA, Kalanetra KM, Haj FG, Karakas S, Oteiza PI. (-)-Epicatechin protects the intestinal barrier from high fat diet-induced permeabilization: implications for steatosis and insulin resistance. Redox Biol. 2018; 14:588–99. https://doi.org/10.1016/j.redox.2017.11.002 PMID: 29154190

66. Ranhotra HS. The estrogen-related receptors in metabolism and cancer: newer insights. J Recept Signal Transduct Res. 2018; 38:95–100. https://doi.org/10.1080/10799893.2018.1456552 PMID: 29619877

67. Afonso MB, Rodrigues PM, Simão AL, Gaspar MM, Carvalho T, Borralho P, Bañales JM, Castro RE, Rodrigues CM. miRNA-21 ablation protects against liver injury and necroptosis in cholestasis. Cell Death Differ. 2018; 25:857–72. https://doi.org/10.1038/s41418-017-0019-x PMID: 29229992

68. Espinosa-Diez C, Miguel V, Vallejo S, Sánchez FJ, Sandoval E, Blanco E, Cannata P, Peiró C, Sánchez-Ferrer CF, Lamas S. Role of glutathione biosynthesis in endothelial dysfunction and fibrosis. Redox Biol. 2018; 14:88–99. https://doi.org/10.1016/j.redox.2017.08.019 PMID: 2888203

69. Han SJ, Choi HS, Kim JI, Park JW, Park KM. IDH2 deficiency increases the liver susceptibility to ischemia-reperfusion injury via increased mitochondrial oxidative injury. Redox Biol. 2018; 14:142–53. https://doi.org/10.1016/j.redox.2017.09.003 PMID: 28938192

70. Aalto AL, Mohan AK, Schwinzer L, Kupka S, Kietz C, Walczak H, Broemer M, Meinander A. M1-linked ubiquitination by LUBEL is required for inflammatory responses to oral infection in Drosophila. Cell Death Differ. 2019; 26:860–76. https://doi.org/10.1038/s41418-018-0164-x PMID: 30026495

71. Flórido A, Saraiva N, Cerqueira S, Almeida N, Parsons M, Batinic-Haberle I, Miranda JP, Costa JG, Carrara G, Castro M, Oliveira NG, Fernandes AS. The manganese(III) porphyrin MnTnHex-2-PyP³⁺ modulates intracellular ROS and breast cancer cell migration:
impact on doxorubicin-treated cells. Redox Biol. 2019; 20:367–78. https://doi.org/10.1016/j.redox.2018.10.016 PMID:30408752

72. Hung CH, Cheng SS, Cheung YT, Wuuwongse S, Zhang NQ, Ho YS, Lee SM, Chang RC. A reciprocal relationship between reactive oxygen species and mitochondrial dynamics in neurodegeneration. Redox Biol. 2018; 14:7–19. https://doi.org/10.1016/j.redox.2017.08.010 PMID:28837882

73. Álvarez-Fernández M, Sanz-Flores M, Sanz-Castillo B, Salazar-Roa M, Partida D, Zapatero-Solana E, Ali HR, Manchado E, Lowe S, VanArsdale T, Shields D, Caldas C, Quintela-Fandino M, Malumbres M. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. Cell Death Differ. 2018; 25:828–40. https://doi.org/10.1038/s41418-018-0024-0 PMID:29229993

74. Hysi PG, Khawaja AP, Menni C, Tamraz B, Wareham N, Khaw KT, Foster PJ, Benet LZ, Spector TD, Hammond CJ. Ascorbic acid metabolites are involved in intraocular pressure control in the general population. Redox Biol. 2019; 20:349–53. https://doi.org/10.1016/j.redox.2018.10.004 PMID:30391827

75. Anderton H, Bandala-Sanchez E, Simpson DS, Rickard JA, Ng AP, Di Rago L, Hall C, Vince JE, Silke J, Liccardi G, Feltham R. RIPK1 prevents TRADD-driven, but TNFR1 independent, apoptosis during development. Cell Death Differ. 2019; 26:877–89. https://doi.org/10.1038/s41418-018-0166-8 PMID:30185824

76. Avalle L, Camporeale A, Morciano G, Caroccia N, Ghetti E, Orecchi V, Viavattene D, Giorgi C, Pinton P, Poli V. STAT3 localizes to the ER, acting as a gatekeeper for ER-mitochondrion Ca2+ fluxes and apoptotic responses. Cell Death Differ. 2019; 26:932–42. https://doi.org/10.1038/s41418-017-0171-y PMID:30042492

77. Fuhrmann DC, Wittig I, Brüne B. TMEM126B deficiency reduces mitochondrial SDH oxidation by LPS, attenuating HIF-1α stabilization and IL-1β expression. Redox Biol. 2019; 20:204–16. https://doi.org/10.1016/j.redox.2018.10.007 PMID:30368040

78. Patel H, Ansari A, Pawara R, Ansari I, Jadhav H, Surana S. Design and synthesis of novel 2,4-disubstituted aminopyrimidines: reversible non-covalent T790M EGFR inhibitors. J Recept Signal Transduct Res. 2018; 38:393–412. https://doi.org/10.1080/10799893.2018.1557207 PMID:31038025

79. Bagati A, Bianchi-Smiraglia A, Moparthy S, Kolesnikova K, Fink EE, Kolesnikova M, Roll MV, Jowdy P, Wolff DW, Polechetti A, Yun DH, Lipchick BC, Paul LM, et al. FOXQ1 controls the induced differentiation of melanocytic cells. Cell Death Differ. 2018; 25:1040–49. https://doi.org/10.1038/s41418-018-0066-y PMID:29463842

80. Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: enhancement of the glyoxalase pathway. Redox Biol. 2018; 14:465–73. https://doi.org/10.1016/j.redox.2017.10.015 PMID:29080525

81. Battistelli C, Sabarese G, Santangelo L, Montaldo C, Gonzalez FJ, Tripodi M, Cicchini C. The IncRNA HOTAIR transcription is controlled by HNF4α-induced chromatin topology modulation. Cell Death Differ. 2019; 26:890–901. https://doi.org/10.1038/s41418-018-0170-z PMID:30154449

82. Peng J, Li Y, Zhou Y, Zhang L, Liu X, Zuo Z. Pharmacophore modeling, molecular docking and molecular dynamics studies on natural products database to discover novel skeleton as non-purine xanthine oxidase inhibitors. J Recept Signal Transduct Res. 2018; 38:246–55. https://doi.org/10.1080/10799893.2018.1476544 PMID:29843539

83. Davidson SM, Arjun S, Basalay MV, Bell RM, Bromage DI, Bøtker HE, Carr RD, Cunningham J, Ghosh AK, Heusch G, Ibanez B, Kleinbongard P, Lecour S, et al. The 10th Biennial Hatter Cardiovascular Institute workshop: cellular protection-evaluating new directions in the setting of myocardial infarction, ischaemic stroke, and cardio-oncology. Basic Res Cardiol. 2018; 113:43. https://doi.org/10.1007/s00395-018-0704-z PMID:30310998

84. Hobson SR, Gurusinginghe S, Lim R, Alers NO, Miller SL, Kingdom JC, Wallace EM. Melatonin improves endothelial function in vitro and prolongs pregnancy in women with early-onset preeclampsia. J Pineal Res. 2018; 65:e12508. https://doi.org/10.1111/jpi.12508 PMID:29766570

85. Staudacher V, Trujillo M, Diederichs T, Dick TP, Radi R, Morgan B, Deponte M. Redox-sensitive GFP fusions for monitoring the catalytic mechanism and inactivation of peroxiredoxins in living cells. Redox Biol. 2018; 14:549–56. https://doi.org/10.1016/j.redox.2017.10.017 PMID:29128826
86. Goiran T, Duplan E, Rouland L, El Manaa W, Lauritzen I, Dunys J, You H, Checler F, Alves da Costa C. Nuclear p53-mediated repression of autophagy involves PINK1 transcriptional down-regulation. Cell Death Differ. 2018; 25:873–84. https://doi.org/10.1038/s41418-017-0016-0 PMID: 29352272

87. Han YS, Kim SM, Lee JH, Jung SK, Noh H, Lee SH. Melatonin protects chronic kidney disease mesenchymal stem cells against senescence via PrPC-dependent enhancement of the mitochondrial function. J Pineal Res. 2019; 66:e12535. https://doi.org/10.1007/s00395-018-0707-9 PMID: 30374170

88. Tabish TA, Zhang S, Winyard PG. Developing the next generation of graphene-based platforms for cancer therapeutics: the potential role of reactive oxygen species. Redox Biol. 2018; 15:34–40. https://doi.org/10.1016/j.redox.2017.11.018 PMID: 29197802

89. Gul-Kahraman K, Yilmaz-Bozoglan M, Sahna E. Physiological and pharmacological effects of melatonin on remote ischemic preconditioning after myocardial ischemia-reperfusion injury in rats: Role of Cybb, Fas, NfkB, Iirisin signaling pathway. J Pineal Res. 2019; 67:e12589. https://doi.org/10.1111/j.12589 PMID: 31155748

90. DeLeon-Pennell KY, Mouton AJ, Ero OK, Ma Y, Padmanabhan Iyer R, Flynn ER, Espinoza I, Musani SK, Vasan RS, Hall ME, Fox ER, Lindsey ML. LXR/RXR signaling and neutrophil phenotype following myocardial infarction classify sex differences in remodeling. Basic Res Cardiol. 2018; 113:40. https://doi.org/10.1007/s00395-018-0699-5 PMID: 30132266

91. Gobert F, Luauté J, Raverot V, Cotton F, Dailler F, Claustrat B, Perrin F, Gronfier C. Is circadian rhythmicity a prerequisite to coma recovery? Circadian recovery concomitant to cognitive improvement in two comatose patients. J Pineal Res. 2019; 66:e12555. https://doi.org/10.1111/j.12555 PMID: 30633817

92. Gandarillas A, Molinuevo R, Sanz-Gómez N. Mammalian endoreplication emerges to reveal a potential developmental timer. Cell Death Differ. 2018; 25:471–76. https://doi.org/10.1038/s41418-017-0040-0 PMID: 29352263

93. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnenmi ES, Altucci L, Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018; 25:486–541. https://doi.org/10.1038/s41418-017-0012-4 PMID: 29362479

94. Gobbi G, Comai S. Sleep well. Untangling the role of melatonin MT1 and MT2 receptors in sleep. J Pineal Res. 2019; 66:e12544. https://doi.org/10.1111/j.12544 PMID: 30586215

95. Edwards KS, Ashraf S, Lomax TM, Wiseman JM, Hall ME, Gava FN, Hall JE, Hosler JP, Harmancey R. Uncoupling protein 3 deficiency impairs myocardial fatty acid oxidation and contractile recovery following ischemia/reperfusion. Basic Res Cardiol. 2018; 113:47. https://doi.org/10.1007/s00395-018-0707-9 PMID: 30374170

96. Frank D, Vince JE. Pyroptosis versus necroptosis: similarities, differences, and crosstalk. Cell Death Differ. 2019; 26:99–114. https://doi.org/10.1038/s41418-018-0212-6 PMID: 30341423

97. Fernández Vázquez G, Reiter RJ, Agil A. Melatonin increases brown adipose tissue mass and function in Zucker diabetic fatty rats: implications for obesity control. J Pineal Res. 2018; 64:e12472. https://doi.org/10.1111/j.12472 PMID: 29405372

98. Tan SW, Yip GW, Suda T, Baeg GH. Small Maf functions in the maintenance of germine stem cells in the Drosophila testis. Redox Biol. 2018; 15:101. https://doi.org/10.1016/j.redox.2017.12.002 PMID: 29245136

99. Galano A, Reiter RJ. Melatonin and its metabolites vs oxidative stress: from individual actions to collective protection. J Pineal Res. 2018; 65:e12514. https://doi.org/10.1111/j.12514 PMID: 29888508

100. Eid RA, Alkhateeb MA, Eleawa S, Al-Hashem FH, Al-Shaim M, El-Kott AF, Zaki MS, Dallak MA, Aldera H. Cardioprotective effect of ghrelin against myocardial infarction-induced left ventricular injury via inhibition of SOCS3 and activation of JAK2/STAT3 signaling. Basic Res Cardiol. 2018; 113:13. https://doi.org/10.1007/s00395-018-0671-4 PMID: 29392420

101. Wang B, Yee Aw T, Stokes KY. N-acetylcysteine attenuates systemic platelet activation and cerebral vessel thrombosis in diabetes. Redox Biol. 2018; 14:218–28. https://doi.org/10.1016/j.redox.2017.09.005 PMID: 28961512

102. Eiringhaus J, Herting J, Schatter F, Nikolaev VO, Sprenger J, Wang Y, Köhn M, Zabel M, El-Armoucha A, Hasenfuss G, Sossalla S, Fischer TH. Protein kinase/phosphatase balance mediates the effects of increased late sodium current on ventricular calcium cycling. Basic Res Cardiol. 2019; 114:13.
103. Denton D, Xu T, Dayan S, Nicolson S, Kumar S. Dpp regulates autophagy-dependent midgut removal and signals to block ecdysone production. Cell Death Differ. 2019; 26:763–78. https://doi.org/10.1038/s41418-018-0154-z PMID:29959404

104. Erland LA, Yasunaga A, Li IT, Murch SJ, Saxena PK. Direct visualization of location and uptake of applied melatonin and serotonin in living tissues and their redistribution in plants in response to thermal stress. J Pineal Res. 2019; 66:e12527. https://doi.org/10.1111/jpi.12527 PMID:30267543

105. Yang T, Cao C, Yang J, Liu T, Lei XG, Zhang Z, Xu S. miR-200a-5p regulates myocardial necroptosis induced by Se deficiency via targeting RNF11. Redox Biol. 2018; 15:159–69. https://doi.org/10.1016/j.redox.2017.11.025 PMID:29248830

106. Gebhard C, Maafi F, Stähli BE, Dang J, Nachar W, de Oliveira Moraes AB, Kernaleguen AE, Lavoie V, Mecteau M, Mihalache D, et al. Apolipoprotein A-I proteolysis in aortic valve stenosis: role of cathepsin S. Basic Res Cardiol. 2018; 113:113:30. https://doi.org/10.1007/s00395-018-0689-7 PMID:29915952

107. Denton D, Kumar S. Autophagy-dependent cell death. Cell Death Differ. 2019; 26:605–16. https://doi.org/10.1038/s41418-018-0252-y PMID:30568239

108. Ding S, Lin N, Sheng X, Zhao Y, Su Y, Xu L, Tong R, Yan Y, Fu Y, He J, Gao Y, Yuan A, Ye L, et al. Melatonin stabilizes rupture-prone vulnerable plaques via regulating macrophage polarization in a nuclear circadian receptor RORα-dependent manner. J Pineal Res. 2019; 67:e12581. https://doi.org/10.1111/jpi.12581 PMID:31009101

109. Zhang B, Hou R, Zou Z, Luo T, Zhang Y, Wang L, Wang B. Mechanically induced autophagy is associated with ATP metabolism and cellular viability in osteocytes in vitro. Redox Biol. 2018; 14:492–98. https://doi.org/10.1016/j.redox.2017.10.021 PMID:29096322

110. Ding M, Ning J, Feng N, Li Z, Liu Z, Wang Y, Wang Y, Li X, Huo C, Jia X, Xu R, Fu F, Wang X, Pei J. Dynamin-related protein 1-mediated mitochondrial fission contributes to post-traumatic cardiac dysfunction in rats and the protective effect of melatonin. J Pineal Res. 2018; 64:64. https://doi.org/10.1111/jpi.12447 PMID:29024001

111. Darido C, Georgy SR, Cullinan C, Partridge DD, Walker R, Srivastava S, Roslan S, Carpinelli MR, Dworkin S, Pearson RB, Jane SM. Stage-dependent therapeutic efficacy in PI3K/mTOR-driven squamous cell carcinoma of the skin. Cell Death Differ. 2018; 25:1146–59. https://doi.org/10.1038/s41418-017-0032-0 PMID:29238073

112. Zhang YH, Wang DW, Xu SF, Zhang S, Fan YG, Yang YY, Guo SQ, Wang S, Guo T, Wang ZY, Guo C. α-Lipoic acid improves abnormal behavior by mitigation of oxidative stress, inflammation, ferroptosis, and tauopathy in P301S Tau transgenic mice. Redox Biol. 2018; 14:535–48. https://doi.org/10.1016/j.redox.2017.11.001 PMID:29126071

113. Hadebe N, Cour M, Lecour S. The SAFE pathway for cardioprotection: is this a promising target? Basic Res Cardiol. 2018; 113:9. https://doi.org/10.1007/s00395-018-0670-5 PMID:29335904

114. Herzog J, Schmidt FP, Hahad O, Mahmoudpour SH, Mangold AK, Garcia Andreo P, Prochaska J, Koeck T, Wild PS, Sørensen M, Daiber A, Münzel T. Acute exposure to nocturnal train noise induces endothelial dysfunction and pro-thromboinflammatory changes of the plasma proteome in healthy subjects. Basic Res Cardiol. 2019; 114:46. https://doi.org/10.1007/s00395-018-0753-y PMID:31664594

115. Heusch G. 25 years of remote ischemic conditioning: from laboratory curiosity to clinical outcome. Basic Res Cardiol. 2018; 113:15. https://doi.org/10.1007/s00395-018-0673-2 PMID:29516255

116. Cieri D, Vicario M, Giacomello M, Vallese F, Filadi R, Wagner T, Pozzan T, Pizzo P, Scorrano L, Brini M, Calì T. SPLICS: a split green fluorescent protein-based contact site sensor for narrow and wide heterotypic organelle juxtaposition. Cell Death Differ. 2018; 25:1131–45. https://doi.org/10.1038/s41418-017-0033-z PMID:29229997