Mitochondrial composition and function under the control of hypoxia

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Abstract

Hypoxia triggers several mechanisms to adapt cells to a low oxygen environment. Mitochondria are major consumers of oxygen and a potential source of reactive oxygen species (ROS). In response to hypoxia they exchange or modify distinct subunits of the respiratory chain and adjust their metabolism, especially lowering the citric acid cycle. Intermediates of the citric acid cycle participate in regulating hypoxia inducible factors (HIF), the key mediators of adaptation to hypoxia. Here we summarize how hypoxia conditions mitochondria with consequences for ROS-production and the HIF-pathway.

1. Introduction

Hypoxia imposes stress to cells and organisms, which occurs under both, pathological and non-pathological conditions. The lack of oxygen is linked to diseases like cancer, diabetes, or inflammation but constitutes also a challenge for people living at high altitude. Cells within organisms adapt to hypoxia by altering their metabolism. This is facilitated by changes in protein expression occurring at the transcriptional or translational level, mRNA- or protein stability as well as enzyme activity. Sensors and adaptors towards decreased oxygen availability are prolylhydroxylases (PHD), also known as Egl nine homolog 1 proteins (EGLN). Their loss of activity stabilizes the transcription factors hypoxia inducible factors (HIF) under hypoxia. HIFs enter the nucleus to enhance transcription of a variety of target genes, including mitochondrial components.

Major consumers of oxygen in the cell are mitochondria. Consequently, they are severely affected by decreased oxygen availability. Along those lines, hypoxia alters mitochondrial fusion and fission, mitophagy, and oxidative phosphorylation (OXPHOS). OXPHOS is adapted to hypoxia by remodeling the electron transport chain (ETC) as well as the activity of the TCA cycle. The mitochondrial respiratory chain was originally described as flavin- and cytochrome-containing proteins in the inner mitochondrial matrix [1]. This model proposed the four major complexes, i.e. NADH-coenzyme Q reductase (complex I), succinate-coenzyme Q reductase or succinate dehydrogenase (complex II or SDH), ubiquinol cytochrome c reductase (complex III), and cytochrome c oxidase (complex IV) of the respiratory chain randomly dispersed in the matrix, being connected by the redox active enzymes coenzyme Q (CoQ) and cytochrome c [2,3]. This model was refined with complex I, III, and IV forming supercomplexes that allow an effective electron transport with a minimum of superoxide (O$_2^-$) production. Nevertheless, ROS (if not specified the term refers to both, superoxide and H$_2$O$_2$) from complex I, II, and III appear not only as an accidental escape of electrons from the ETC and their transfer to molecular oxygen, but are now considered as important mediators in physiological cell signaling. ROS production needs to be tightly controlled to avoid its overproduction, provoking damage of mitochondrial and extramitochondrial macromolecules and eliciting cell death [4]. Considering that ROS signaling is linked to the HIF system, it allows anticipating multiple layers of reciprocal interaction. Each ETC complex adapts to hypoxia by replacing distinct proteins, which alter the function of the complex. Using this system, it is not necessary to build an entire new complex to adapt, making these processes fast, reversible, and highly effective. Another adaptive response to hypoxia is the reduction of mitochondrial mass, by mitophagy [5]. This specialized form of autophagy involves factors such as nucleoporin p62, beclin1, microtubule-associated protein1A/1B-light chain 3 (LC3), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), or BNIP3 ligant [6,7]. These components are part of the phosphatidylinositide 3-kinase class III complex-mediated autophagosome formation. The autophagosome docks to lysosomes, followed by fusion and subsequent digestion of trapped macromolecules/organelles. Some proteins eliciting autophagosome formation like BNIP3 are HIF-regulated, suggesting that mitophagy under hypoxia is at least partly HIF-driven [8–10]. In this review, we address fundamental changes and adaptive mechanisms of mitochondria and mitochondrial ROS production to hypoxia and refer to the crosstalk between mitochondria and the HIF-system (Fig. 1).
2. Mitochondrial ROS production in brief

Besides NADPH oxidases, mitochondria emerged as a powerful source of ROS. Fig. 2 provides an overview towards ROS-production by the ETC and ROS-detoxifying enzymes. Deficiencies in assembling ETC components, mutations in distinct ETC subunits, or the specific inhibition of the ETC can increase ROS production. The molecular details of ROS production at distinct ETC complexes are elaborated in review articles [11–16]. Individual targets, experiencing oxidative modifications in response to complex I and III ROS have been identified [17]. Complex I ROS oxidize TCA cycle associated proteins like subunits of pyruvate dehydrogenase or isocitrate dehydrogenase as well as 2-oxoglutarate dehydrogenase complex component E2 [17]. Apparently, complex I ROS are predominantly oxidizing proteins that are localized in the matrix. Complex III ROS in turn oxidize proteins such as voltage-dependent anion channel 3 and mitochondrial import inner membrane translocase subunit TIM50 but also NDUFB10 and NDUFS3, both components of complex I, which are located in the mitochondrial inner membrane [17]. The voltage-dependent anion channel 3 in the outer mitochondrial membrane was proposed as a marker for oxidative stress, occurring in the intermembrane space [18]. Conclusively, distinct sources of ROS modify divergent proteins and thus, alter discrete signaling pathways (Fig. 3).

3. Regulation of HIF

HIF proteins are key determinants of a cellular response to hypoxia. Once stabilized, they induce multiple target genes, thereby affecting intermediary metabolism e.g. by increasing the expression of proteins involved in glycolysis and decreasing oxygen-dependent pathways by altering the ETC complex structure and activity. The fundamental concepts of HIF regulation are outlined in Fig. 4.

4. Fusion and fission

Besides changes at the protein level, that affect the quarterly structure of protein aggregates, hypoxia impacts on the mitochondrial morphology, including cristae structure (Fig. 5) [19]. Under normoxia, mitochondria form tubular networks favoring OXPHOS and ATP production. Under hypoxia, mitochondria undergo fission and appear as single organelles, possibly to promote mitophagy, to keep ROS production at a physiological low level, and to maintain integrity by a decrease in respiratory activity.

5. Crosstalk between HIF and mitochondria

Ongoing research in the areas of metabolomics, assembly, and structure of ETC components provide multiple links between mitochondria and the HIF pathway, as depicted in Fig. 6. HIF gets stabilized by a decreased PHD activity, an enzyme demanding metabolites of the mitochondrial TCA cycle for catalysis. In turn, HIF induces the expression of proteins, which impinge on both, metabolism and structure of mitochondria as described in detail in the following figures.
6. Adaptation of the respiratory chain to hypoxia

ROS generation is a tightly controlled process and has pivotal roles in patho-physiological signaling. Thus, adaptation processes have evolved to maintain mitochondrial membrane potential and ATP production, at the same time avoiding uncontrolled ROS production. This becomes obvious when oxygen availability declines. A lack of oxygen induces reductive carboxylation, which was shown to increase antioxidant capacities. For example, a high ROS production rate causes cell death, while moderate ROS levels provoke cytokine production (inflammation). Importantly, spatial and subcellular ROS production by mitochondria and NADPH oxidases create oxidative microenvironments within the cell, affecting distinct proteins or organelles. This review focuses on mitochondrial ROS in connection with hypoxic adaptation. Fig. 3 shows several proteins (blue), which are influenced by ROS (inner heptagon), and their role in cellular signaling (outer ring). Abbreviations: Ask1: apoptosis signal-regulating kinase 1, ATM: ataxia telangiectasia mutated, Cytc: cytochrome c, IRP: iron-related protein, NADPH: nicotinamide adenine dinucleotide phosphate, NDUFV10: NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10, NDUFV5: NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 1, NDUFB10: NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10, NDUFS3: NADH dehydrogenase [ubiquinone] 1 iron-sulfur protein 3, NFkB: nuclear factor (NF) kappa B, Nrf2: Nuclear factor (erythroid-derived 2)-like 2, Nrf2: Nuclear factor erythroid derived 2, p53: cellular tumor antigen p53, PTP: phosphatidylinositol 3-kinase, PTP: protein-tyrosine phosphatase, ROS: reactive oxygen species, Shc: SHC-transforming protein, SOD: superoxide dismutase, TIM50: mitochondrial import inner membrane translocase subunit TIM50, VDAC: voltage-dependent anion channel.

after reoxygenation provoking a decrease in protein stability [24]. Another form of oxidative stress sensed and handled predominantly by mitochondria is ischemia and reperfusion (I/R). During I/R an oxidative burst occurs, which is generated by enhanced succinate dehydrogenase activity and Ca^{2+} influx, which opens the mitochondrial permeability transition pore. An overview of ROS generating mechanisms and consequences of I/R is depicted in Fig. 9.

7. Conclusion

Research over the last decades highlighted the impact of hypoxia on mitochondria and mitochondrial metabolism, including changes in ROS production and signaling. It is becoming apparent that ETC complexes adapt by posttranslational modification of distinct proteins in individual complexes or by altering subunit composition to keep

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**Fig. 3.** ROS in cellular signalling. The picture of ROS has changed within the last decades from being considered a harmful substance to an important signaling molecule [30]. Especially mitochondrial-derived ROS are mediators of diverse signaling pathways to provoke immune response, elicit antioxidative signaling, initiate DNA damage responses, affect iron homeostasis, stimulate apoptosis, or signal towards cell survival and proliferation [31–33]. The apparently contradictory roles linked to ROS signaling can be explained by the distinct species, amount, and duration of ROS production as well as antioxidative capacities. For example, a high ROS production rate causes cell death, while moderate ROS levels provoke cytokine production (inflammation). Importantly, spatial and subcellular ROS production by mitochondria and NADPH oxidases create oxidative microenvironments within the cell, affecting distinct proteins or organelles. This review focuses on mitochondrial ROS in connection with hypoxic adaptation. Fig. 3 shows several proteins (blue), which are influenced by ROS (inner heptagon), and their role in cellular signaling (outer ring). Abbreviations: Ask1: apoptosis signal-regulating kinase 1, ATM: ataxia telangiectasia mutated, Cytc: cytochrome c, IRP: iron-related protein, NADPH: nicotinamide adenine dinucleotide phosphate, NDUFV10: NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10, NDUFS3: NADH dehydrogenase [ubiquinone] 1 iron-sulfur protein 3, NFkB: nuclear factor (NF) kappa B, Nrf2: Nuclear factor (erythroid-derived 2)-like 2, Nrf2: Nuclear factor erythroid derived 2, p53: cellular tumor antigen p53, PTP: phosphatidylinositol 3-kinase, PTP: protein-tyrosine phosphatase, ROS: reactive oxygen species, Shc: SHC-transforming protein, SOD: superoxide dismutase, TIM50: mitochondrial import inner membrane translocase subunit TIM50, VDAC: voltage-dependent anion channel.

**Fig. 4.** Basics of the HIF-system. Under hypoxic conditions HIF is a master regulator for adaptation to low oxygen content and causes the expression of roughly 400 target genes [34]. The heterodimeric transcription factor consists of the constitutively expressed HIF-1β also known as ARNT and a labile α-subunit, belonging to the basic helix-loop-helix/Per ARNT SIM transcription factor family. Three HIF-α isoforms are known in mammals. HIF-1α and HIF-2α share high sequence homology and regulatory features, containing an oxygen-dependent degradation domain, with two conserved prolyl residues [35]. Under normoxia the α-subunit prolyl residues are continuously hydroxylated by PHD 1–3. This reaction is catalyzed by a set of non-haem Fe(II)- and 2-oxoglutarate-dependent dioxygenases. During catalysis, the splitting of molecular oxygen is coupled to the hydroxylation of HIF, while the oxidative decarboxylation of 2-oxoglutarate gives succinate and CO2. PHDs are inhibited (I) by the lack of oxygen or metabolites such as fumarate or succinate (further information in Fig. 6). Following hydroxylation, pVHL binds and marks HIF for ubiquitination and thus, proteasomal degradation [36–38]. Under hypoxic conditions, PHDs are inhibited, HIF-α gets stabilized, translocates to the nucleus, dimerizes with its corresponding β-subunit, and recognizes HREs within a promoter or enhancer of distinct target genes to initiate transcription by recruitment of cofactors like p300 or CBP [39,40]. Inactivation of PHD enzymes may be promoted by ROS e.g. due to oxidation of the central Fe(II) to Fe(III), especially if the antioxidative capacity of the cell is low. It remains a matter of discussion to define concentrations, distinct ROS species and/or secondary metabolites that interfere with PHD activity. Recent studies revealed that PHDs are not only sensitive to iron oxidations but also contain redox-sensitive cysteines, which are subjected to multiple modifications. This highlights diverse possibilities of PHD activity regulation and thus HIF stabilization [41]. Abbreviations: ARNT: Aryl hydrocarbon receptor nuclear translocator, CBP: CREB-binding protein, HIF: hypoxia inducible factor, HRE: hypoxia response element, p300: histone acetyl transferase p300, PHD: prolyl hydroxylase, pVHL: tumor suppressor protein von Hippel-Lindau, ROS: reactive oxygen species.
ROS production at a low, physiological level (Fig. 10). However, cell type specific responses, the presence of various amounts of detoxifying components and ROS-facilitated oxidation in micro-compartments such as the inner membrane space versus the inner mitochondrial membrane or the mitochondrial matrix make it difficult to generalize observations. Another issue of controversy is stabilization of HIF by mitochondrial ROS and the production of ROS under hypoxia itself. Very likely, the different mechanisms that allow adaption of the ETC complexes to hypoxia evolved to keep ROS at a balanced level. Low physiological mitochondrial ROS are needed to guarantee cytokine formation during defense against invading pathogens, at the same time keeping mitochondrial integrity intact, e.g. avoiding destruction of mitochondrial DNA, lipids, or macromolecules [25]. Moreover, adaptation may preserve other functions of mitochondria during intermediary metabolism, like amino acid metabolism or the delivery of building blocks needed for cell proliferation under hypoxia. The advantage of
Subcomplex subunit 4-like 2, ROS: reactive oxygen species

Subcomplex subunit 9, NDUFA4L2: NADH dehydrogenase [ubiquinone] 1 alpha oxidoreductase chain 5, NDUFA9: NADH dehydrogenase [ubiquinone] 1 alpha oxidoreductase chain 1, ND3: NADH-ubiquinone oxidoreductase.

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**Fig. 7.** Hypoxic adaptation of complex I. A NDUFA4L2 decreases complex I activity: NDUFA4L2 was characterized by Tello et al. as a HIF-1 target gene, which reduced complex I activity under hypoxic conditions [73]. Induction of NDUFA4L2 under hypoxia decreased respiration, prevented an increase in ROS production and preserved the membrane potential. Lai et al. confirmed the HIF-1-dependent induction of NDUFA4L2 and connected its enhanced expression in hepatocellular carcinoma to poor patient survival [74]. Along those lines, a knockdown of NDUFA4L2 suppressed tumor growth as well as metastasis in vivo. B miR-210 decreases ISCU: miR-210 is an established HIF-target and one of the major regulators of metabolism under hypoxia [75,76]. Furthermore, miR-210 reduces levels of complex I and IV together with their enzyme activity [77]. Thus, it is not surprising that miR-210 plays a central role in regulating ETC complex formation. Importantly, miR-210 attenuates ISCU [78,79]. ISCU functions as a scaffold for maturation of iron-sulfur containing proteins, such as NDUFS in complex I. A defect in an iron-sulfur containing protein disrupts the electron flow within this complex. Thus, a miR-210-mediated decrease in ISCU induces ROS formation under hypoxia [80]. Both, NDUFA4L2 and ISCU are HIF-regulated proteins. While NDUFA4L2 is decreased by miR-210, Interestingly, they have opposing roles in ROS production. NDUFA4L2 induction decreases ROS, but a reduction of ISCU increases ROS formation. These findings underscore the relevance of the site for ROS production and highlight the difficulties in predicting how modifications or differently composed ETC complexes affect ROS production. C Hypoxia provokes complex I transition: Under hypoxia, respectively during ischemia, complex I changes its conformation from the active (A) to the dormant (D) form [81]. The D-form is considered to be silent in terms of ROS formation and thus, does not create a burst in ROS following reoxygenation [82]. The precise mechanism is not fully understood, but the proteins NDUFA9, ND1, and ND3 at the connection of the membrane arm of complex I, apparently are involved [83]. After I/R, CysS9 of NDS is exposed and can be S-nitrosated by different S-nitrosating species, maintaining complex I in the D-form and reducing ROS production under reoxygenation [84]. Other proteins of the membrane arm, ND4 and ND5, were decreased under hypoxia at mRNA level, decreasing complex I activity [85]. Raising the question whether those subunits might also be involved in complex I transition. Abbreviations: ETC: electron transport chain, HIF: hypoxia inducible factor, HRE: hypoxia response element, I/R: ischemia/reperfusion, ISCU: iron sulfur cluster assembly enzyme, miR: micro RNA, ND1: NADH-ubiquinone oxidoreductase chain 1, ND3: NADH-ubiquinone oxidoreductase chain 3 ND4: NADH-ubiquinone oxidoreductase chain 4, ND5: NADH-ubiquinone oxidoreductase chain 5, NDUFA9: NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, NDUFA4L2: NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4-like 2, ROS: reactive oxygen species.

**Fig. 8.** Hypoxic adaptation of complex II and IV. A Complex II: As part of the TCA cycle and the respiratory chain complex II (succinate dehydrogenase) is integral to mitochondrial metabolism. HIF-1, via the induction of miR-210, modulates complex I, as described in Fig. 7 [86]. In addition, miR-210 targets SDHD, one of the membrane bound and haem b containing subunits of complex II [87]. In A549 cells transfected with miR-210 SDHD expression decreased, accompanied by a lower complex II activity. Recent studies identified complex II, besides complex I and III, as a generator of ROS, opening the possibility that complex II serves as an additional regulator of ROS under hypoxia [88]. B miR-210 regulates complex IV abundance and activity: Besides ISCU and SDHD, the complex IV subunit COX10 was identified as a miR-210 target either by transfecting HCT116 cells with miR-210 under normoxia or with an antagonist under hypoxia [89]. These experiments linked miR-210 expression to increased ROS production. Moreover, a screening approach also identified NDUFA4 as a miR-210 regulated complex IV subunit [87,90]. C Subunit exchange in complex IV: Complex IV is regulated by a HIF-dependent exchange of its subunits COX4-1 and COX4-2 under hypoxic conditions [91]. HIF-1 induces COX4-2 together with the Lon protease, which in turn degrades COX4-1. The complex subsequently incorporates COX4-2. This modification optimizes the efficiency of the complex to transfer electrons to molecular oxygen under low oxygen conditions and, thus, to decrease ROS formation, maintain ATP production, and to preserve the integrity of complex IV. D HIGD1A enhances complex IV activity: As an early hypoxic inducible and HIF-dependent protein, HIGD1A apparently amalgamates many functions as already described for its function in fusion and fission. Among others, it ensures optimal performance of complex IV [92]. Hayashi et al. showed that HIGD1A binds to complex IV in vivo, while recombiant HIGD1A directly integrated into purified bovine complex IV. Precisely, HIGD1A exerts a protective function. It accumulated around the haem a containing active center of complex IV, a protein cluster, which is responsible for the proton pumping activity of complex IV. E COX5B decreases HIF-1-dependently. In white adipose tissue COX5B decreases during aging due to HIF-1α mediated transcriptional repression [93]. The lack of COX5B decreases complex IV assembly and activity. Additionally, inhibition of COX5B facilitated lipid accumulation by a reduction in fatty acid oxidation, which in turn enlarged white adipocytes. Abbreviations: COX4: cytochrome c oxidase subunit 4, COX5B: cytochrome c oxidase subunit 5B, COX10: proteoheme IX farnesyltransferase, ETC: electron transport chain, HIF: hypoxia inducible factor, HIGD1A: hypoxia inducible gene 1, HRE: hypoxia response element, Lon: Lon protease homolog, ISCU: iron sulfur cluster assembly enzyme, miR: micro RNA, NDUFA4: NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4, PHD: prolyl hydroxylase, ROS: reactive oxygen species, SDHD: succinate dehydrogenase [ubiquinone] cytochrome b small subunit, TCA: citric acid cycle.
Mitochondrial ROS production cannot only be seen as an accidental escape of electrons from the ETC and its transfer to molecular oxygen with the production of superoxide and/or hydrogen peroxide but should also be considered an essential component of physiological cell communication. In a hypoxic environment, often found in tumors, mitochondrial biology is altered. It is generally accepted that OXPHOS is slowed down because reducing equivalents generated in the TCA cycle are decreasing. Nevertheless, hypoxia massively modulates ETC composition and activity. Interestingly, hypoxia, mostly via the HIF-transducing system, produces subtle changes by modifying individual proteins in complex I to IV or by replacing distinct proteins with either more effective (e.g. complex IV) or less efficient (e.g. complex I) variants. Energetically, this is more efficient rather than replacing entire ETC complexes and probably allows a much faster return to basal complex composition when returning to normoxia. Overall, these changes adjust the ability of ROS production under hypoxia, often reducing the ability to generate ROS. It can be speculated that under hypoxia, despite a reduced electron flow through the individual redox centers, mitochondria try to minimize ROS formation in order to lower the risk of macromolecular damage. One can also argue that changes are preventive in order to suppress a burst in ROS once mitochondria return from hypoxia back to normoxia. Along these lines, mitochondrial fission certainly may eliminate damaged mitochondria that often show increased ROS production. Fission observed during hypoxia may be considered as a preventive mechanism to lower ROS production and to exit to mitophagy once environmental conditions get worse or to fuse when mitochondria face normoxia again. We certainly have to learn more about the communicating ability and distinct targets of ROS under hypoxia and explore how a gradual and time-dependent decrease of oxygen affects mitochondrial biology and what happens upon the shift from hypoxia back to normoxia. Abbreviations: ETC: electron transport chain, HIF: hypoxia inducible factor, HIGD1A: hypoxia inducible gene 1, OXPHOS: oxidative phosphorylation, ROS: reactive oxygen species, TCA: citric acid cycle.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] D.E. Green, A. Tzagoloff, The mitochondrial electron transfer chain, Arch. Biochem. Biophys. 116 (1966) 293–304.
[2] B. Chance, G.R. Williams, A method for the localization of sites for oxidative phosphorylation, Nature 176 (1955) 250–254.
[3] T. Friedrich, B. Bottcher, The gross structure of the respiratory complex I: a lego system, Biochim. Biophys. Acta 1608 (2004) 1–9.
[4] G.S. Shadel, T.L. Horvath, Mitochondrial ROS signaling in organismal homeostasis, Cell 163 (2015) 560–569.
[5] D.C. Fuhrmann, I. Wittig, H. Heide, N. Dehne, B. Brune, Chronic hypoxia alters mitochondrial composition in human macrophages, Biochim. Biophys. Acta 1834 (2013) 2750–2760.
[6] M.C. Mairui, T. Salkicvar, A. Kimchi, G. Kroemer, Self-eating and self-killing: crosstalk between autophagy and apoptosis, Nat. Rev. Mol. Cell Biol. 8 (2007) 741–752.
[7] D.A. Kubi, A.B. Gustafsson, Mitochondria and mitophagy: the yin and yang of cell
death control, Circ. Res. 112 (2013) 1208–1221.
[8] G. Bellot, R. Garcia-Medina, P. Gouon, J. Chiche, D. Roux, J. Pouysegu, N.M. Mazure, Hypoxia-induced autophagy is mediated through hypoxia-inducible factor 1alpha (HIF-1alpha) and HIF-1beta via their HRE domains, Mol. Cell. Biol. 29 (2009) 2570–2581.
[9] H. Zhang, M. Bosch-Marce, L.A. Shioda, Y.S. Tan, J.H. Baek, J.B. Wesley, F.J. Gonzalez, G.L. Semenza, Mitochondrial autophagy is an HIF-1-dependent mechanism to metabolic stresses to hypoxia, J. Biol. Chem. 283 (2008) 16982–16992.
[10] R. Anand, T. Langer, J.M. Gleadle, P.J. Ratcliffe, Activation of apoptosis signalling pathways by reactive oxygen species in cell signaling pathways and immune responses to viral infections, Arch. Virol. (2016).
[11] H. Kim, M.C. Scimia, D. Wilkinson, R.D. Trelles, M.R. Wood, D. Bowtell, A. Dillin, M. Merola, Z.A. Ronai, Fine-tuning of Drp1/Fis1 availability by AKAP12/Slh2 regulates mitochondrial adaptation to hypoxia, Mol. Cell 44 (2011) 532–544.
[12] K. Nakayama, I.J. Frew, M. Hagensen, M. Skals, H. Habelah, A. Blomquist, T. Kadya, E. Hrdjumana, C. Wirth, U. Brandt, C. Hunte, V. Zickermann, Structure and function of mitochondrial complex I, Biochim. Biophys. Acta 1856 (2016) 384–392.
[13] H. Kim, I. Wittig, H. Blagih, E. Amir, M. Clemons, A. Aguilar-Mahecha, M. Asagiri, Y. Yamaguchi, M. Miura, D.M. Jenkins, H. Choi, J.W. Kim, M. Asagiri, Y. Qian, Y. Li, X. Huang, Z. Ronai, Siah2 regulates stability of prolyl-hydroxylases, controls HIF/HIFalpha abundance, and modulates physiological responses to hypoxia, Cell 117 (2004) 941–952.
[14] X.J. Han, J.Z. Yang, L.P. Jiang, Y.F. Wei, Q.N. Lai, J.R. Wang, B.H. Xin, J.X. Han, Involvement of Drp1 in hypoxia-induced migration of human glioblastoma U251 cells, Oncol. Rep. 32 (2014) 619–626.
[15] H. Jin, Z. Yang, L.P. Jiang, Y.F. Wei, M.P. Liao, Y. Qian, Y. Li, X. Huang, J.R. Wang, B.H. Xin, Y. Yang, Mitochondrial dynamics regulates hypoxia-induced migration and antiangiogenic activity of cisplatin in breast cancer cells, Int. J. Oncol. 46 (2015) 691–700.
[16] D. Santos, A.R. Esteves, D.F. Silva, C. Januario, S.M. Cardoso, The impact of mitochondrial fusion and fission on glutathione metabolism in sporadic Parkinson’s disease, Mol. Neurobiol. 52 (2015) 573–586.
[17] T. Landes, L.J. Emerone, D. Courilleau, M. Rojo, P. Belenguer, L. Arnaune-Pelloquin, The BH3-only Bnip3 binds to the dynamin Opal1 to promote mitochondrial fragmentation and apoptosis by distinct mechanisms, EMBO Rep. 11 (2010) 459–465.
[18] N. Wang, X. Hu, L. Zhu, H. Gu, Z. Gao, P. Gao, D. Bowtell, A. Dillin, M. Asagiri, Y. Yamaguchi, M. Miura, D.M. Jenkins, H. Choi, J.W. Kim, M. Asagiri, Y. Qian, Y. Li, X. Huang, Z. Ronai, Siah2 regulates stability of prolyl-hydroxylases, controls HIF/HIFalpha abundance, and modulates physiological responses to hypoxia, Cell 117 (2004) 941–952.

P.J. Ratcliffe, J.M. Gleade, Differential function of the prolyl hydroxylases PHD1, PHD2, and PHD3 in the regulation of hypoxia-inducible factor, J. Biol. Chem. 279 (2004) 38458–38465.

N. Fujita, D. Markova, D.G. Anderson, K. Chiba, Y. Toya, J.M. Shapiro, M.V. Rusbud, Expression of prolyl hydroxylases (PHDs) is selectively controlled by HIF-1 and HIF-2 proteins in nucleus pulposus cells of the intervertebral disc: distinct roles of PHD2 and PHD3 proteins in controlling HIF-1alpha activity in hypoxia, J. Biol. Chem. 280 (2005) 16982–16992.

A. Sugars, S. Jana, C.P. Furlinger, J. Wang, A.S. Sagona, E. Tschudy, A. Soares, E. Ghasri, S. Sato, S. Dorman, P. Kroemer, M. Dittmar, J. Flad, D. Krstic, M. van der Merwe, K. Dohmae, J. Sonnenberg, R. Stambolic, J. Francke, A. Hirsch, A. Dillin, T. Langer, J.M. Gleadle, P.J. Ratcliffe, Activation of mitophagy by prolyl hydroxylase inhibitors to recover from metabolic stress, Nat. Commun. 7 (2016) 11635.

F. Dupuy, S. Tabaries, A. Alzuy, Z. Jiang, X. Wang, A. Dillin, M. Asagiri, Y. Yamaguchi, M. Miura, D.M. Jenkins, H. Choi, J.W. Kim, M. Asagiri, Y. Qian, Y. Li, X. Huang, Z. Ronai, Siah2 regulates stability of prolyl-hydroxylases, controls HIF/HIFalpha abundance, and modulates physiological responses to hypoxia, Cell 117 (2004) 941–952.

H. Liu, C.L. Dalgard, A. Mohyeldin, T. McFate, A.S. Tait, A. Verma, Reversible inactivation of HIF-1alpha by hydroxylase inhibitors allows cell metabolism to control basal expression of prolyl hydroxylase inhibitors, Nat. Chem. Biol. 26 (2007) 4524–4532.

H. Liu, C.L. Dalgard, A. Mohyeldin, T. McFate, A.S. Tait, A. Verma, Reversible inactivation of HIF-1alpha by hydroxylase inhibitors allows cell metabolism to control basal expression of prolyl hydroxylase inhibitors, Nat. Chem. Biol. 26 (2007) 4524–4532.

H. Liu, C.L. Dalgard, A. Mohyeldin, T. McFate, A.S. Tait, A. Verma, Reversible inactivation of HIF-1alpha by hydroxylase inhibitors allows cell metabolism to control basal expression of prolyl hydroxylase inhibitors, Nat. Chem. Biol. 26 (2007) 4524–4532.
D. Tello, E. Balsa, B. Acosta-Iborra, E. Fuertes-Yebra, A. Elorza, A. Ordonez, Y.L. Chua, E. Dufour, E.P. Dassa, P. Rustin, H.T. Jacobs, C.T. Taylor, T. Hagen, M. Babot, A. Birch, P. Labarbuta, A. Galkin, Characterisation of the active/de-active transition of mitochondrial complex I, Biochim. Biophys. Acta 1837 (2014) 1083–1092.

S. Drose, A. Stepanova, A. Galkin, Ischemic A/D transition of mitochondrial complex I and its role in ROS generation, Biochim. Biophys. Acta 1857 (2015) 946–957.

M. Ciano, M. Fuxgard, H. Heide, C.H. Botting, A. Galkin, Conformation-specific croslinking of mitochondrial complex I, FEBS Lett. 587 (2013) 867–872.

E.T. Chouchani, C. Methner, S.M. Nadtochiy, A. Logan, V.R. Pell, S. Ding, A.M. James, H.M. Cocheme, J. Reinhold, K.S. Lilley, L. Partridge, I.M. Fearnley, A.J. Robinson, R.C. Hartley, R.A. Smith, T. Krieg, P.S. Brooks, M.P. Murphy, Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I, Nat. Med. 19 (2013) 753–756.

J.P. Piriat, J. Lopez-Barneo, Oxygen tension regulates mitochondrial DNA-encoded complex I gene expression, J. Biol. Chem. 280 (2005) 42676–42684.

C. Devlin, S. Greco, M. Ivan, miR-210: more than a silent player in hypoxia, IUBMB Life 63 (2011) 94–100.

M.P. Puissegur, N.M. Mazure, T. Bertero, L. Pradelli, S. Grosso, K. Robbe-Semsret, T. Maurin, K. Lebrignon, B. Cardinal, V. Hofman, S. Foure, V. Magioni, J.E. Rici, J. Pouyssegur, P. Gounon, P. Hofman, P. Barrey, B. Mari, miR-210 is overexpressed in late stages of lung cancer and mediates mitochondrial alterations associated with modulation of HIF-1 activity, Cell Death Differ. 18 (2011) 465–478.

C.L. Quinlan, L.V. Pervoshchikova, M. Hey-Mogens, A.L. Orr, M.D. Brand, Sites of reactive oxygen species generation by mitochonodria oxidizing different substrates, Redox Biol. 1 (2013) 304–312.

Z. Chen, Y. Li, H. Zhang, P. Huang, R. Luthra, Hypoxia-regulated microRNA-210 modulates mitochondrial function and decreases ISCU and CoxOx1 expression, Oncogene 29 (2010) 4362–4368.

E. Balsa, R. Marco, E. Perales-Clemente, R. Szklarczyk, E. Calvo, M.O. Landazuri, J.A. Enriquez, C. Blick, J. Ragoussis, J. Schoedel, D.R. Mole, A.C. Young, X. Yue, P. Zhao, K. Wu, J. Huang, W. Zhang, Y. Wu, X. Liang, X. He, GRIM-19 binds to HIF-1alpha and stabilizes it, PLoS Genet. 8 (2012) e1002601.

B. Brune, N. Dehne, Sensors, transmitters and targets in mitochondrial oxygen metabolism, Cold Spring Harb. Symp. Quant. Biol. 76 (2011) 487–753.

G.L. Semenza, Regulation of metabolism by hypoxia-inducible factor 1, Cold Spring Harb. Symp. Quant. Biol. 76 (2011) 1–9.

G.L. Semenza, Oxygen-dependent regulation of mitochondrial respiration by hypoxia-inducible factor 1, Biochem. J. 405 (2007) 1–9.

D. B. Brunet, N. Dehne, Sensors, transmitters and targets in mitochondrial oxygen shortage - A HIF relay story, Antioxid. Redox Signal.

P. Hernansanz-Aguin, A. Izuqiero-Alvarez, P.J. Sanchez-Getema, E. Ramos, E. Fuertes-Yebra, A. Elorza, A. Ordonez, T. Villa-Pina, S. Lamas, A. Boglanova, A. Martinez-Ruiz, Active hypoxia promotes a superoxide burst in cells, Free Radic. Biol. Med. 71 (2014) 146–156.

R.D. Guzy, B. Sharma, E. Bell, N.S. Chandel, P.T. Schumacker, Loss of the SdhB, but not the SdhA, subunit of complex II triggers reactive oxygen species-dependent hypoxia-inducible factor activation and tumorigenesis, Med. Cell. Biol. 28 (2008) 718–731.

X. Yue, P. Zhao, K. Wu, J. Huang, W. Zhang, Y. Wu, X. Liang, X. He, GRIM-19 inhibition induced autophagy through activation of ERK and HIF-1alpha not STAT3 in Hela cells, Tumour Biol. 37 (2016) 9795–9796.

Y. Saito, K.A. Ishii, Y. Aita, T. Ikeda, Y. Kawakami, H. Shimano, H. Hara, K. Takekoshi, Loss of SdhB elevates catecholamine synthesis and secretion depending on ROS production and HIF stabilization, Neurochem. Res. 41 (2016) 696–706.

G. Comito, M. Calvani, E. Giannoni, F. Bianchini, L. Calori, E. Gali, C. Migliore, R.I. McCormick, C. Blick, J. Ragoussis, J. Schoedel, D.R. Mole, A.C. Young, X. Yue, P. Zhao, K. Wu, J. Huang, W. Zhang, Y. Wu, X. Liang, X. He, GRIM-19 binds to HIF-1alpha and stabilizes it, PLoS Genet. 8 (2012) e1002601.

R. Fukuda, H. Zhang, J.W. Kim, L. Shimoda, C.V. Dang, G.L. Semenza, HIF-1 regulates cytochrome oxidase subunits to optimize efficiency of respiration in hypoxic cells, Cell 129 (2007) 111–122.

T. Hayashi, Y. Asano, Y. Shintani, H. Aoyama, H. Kidoa, O. Tunkamoto, M. Hikita, K. Shimazawa-Isho, T. Katakaji, S. Higo, H. Kato, S. Yamazaki, M. Katsusaka, A. Nakano, H. Anasumas, H. Makura, T. Minamino, Y. Goto, T. Ogura, M. Kitakaze, I. Komuro, Y. Sakata, T. Tsukihara, S. Yoshikawa, S. Takashima, HigG1 is a positive regulator of cytochrome c oxidase, Proc. Natl. Acad. Sci. USA 112 (2015) 1553–1558.

I. Soro-Armaz, Q.O. Li, M. Torres-Capelli, F. Melendez-Rodriguez, S. Veiga, K. Veys, D. Sebastian, A. Elorza, T. Dello, P. Hernansanz-Aguin, S. Cogliati, J.M. Moreno-Navarrete, E. Balsa, E. Fuertes, E. Romanos, A. Martinez-Ruiz, J.A. Enriquez, J.M. Fernandez-Real, A. Zorzano, K. De Bock, J. Aragones, Role of mitochondrial complex IV in age-dependent obesity, Cell Rep. 16 (2016) 2991–3002.

E.T. Chouchani, V.R. Pell, E. Gaude, A. Ksentintiev, S.Y. Sundier, E.L. Robb, A. Logan, S.M. Nadtochiy, E.N. Ord, A.C. Smith, F. Eyassu, R. Shirley, C.H. U., A.J. Dare, A.M. James, S. Rogatti, J.C. Hartley, S. Eaton, A.S. Costa, P.S. Brooks, S.M. Davidson, M.R. Duchen, K. Saeb-Parsy, M.J. Shattock, A.J. Robinson, L.M. Work, C. Frezza, T. Krieg, M.P. Murphy, Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS, Nature 515 (2014) 431–435.

S. Jang, T.S. Lewis, C. Powers, Z. Khuchua, C.P. Baines, P. Wipf, S. Javadov, Elucidating mitochondrial electron transport chain supercomplexes in the heart during ischemia-reperfusion, Antioxid. Redox Signal. (2016).

H. Kamata, S. Honda, S. Maeda, L. Chang, H. Hirata, M. Karin, Reactive oxygen species promote TNF alpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases, Cell 120 (2005) 649–661.

J. Sun, G. Sun, X. Meng, H. Wang, M. Qin, M. Bin, Y. Luo, Y. Yu, R. Chen, Q. Ai, X. Sun, Ginsenoside Rk3 prevents hypoxia-reoxygenation induced apoptosis in H9c2 cardiomyocytes via AKT and MAPK pathway, Evid. Based Complement. Altern. Med. 2013 (2013) 690190.

F. Bagheri, V. Khorri, A.M. Alizadeh, S. Khalighfard, S. Khodayari, H. Khodayari, Reactive oxygen species-mediated cardiac-reperfusion injury: mechanisms and therapies, Life Sci. 165 (2016) 43–55.

N.B. Madhungr, N.F. Zilberstein, Y. Feng, J.C. Bopassa, Critical role of mitochondrial ROS is dependent on their site of production on the electron transport chain in ischemic heart, Am. J. Cardiovasc. Dis. 6 (2016) 93–108.