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Interplay between hypoxia inducible Factor-1 and mitochondria in cardiac diseases

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ABSTRACT

Ischemic heart diseases and cardiomyopathies are characterized by hypoxia, energy starvation and mitochondrial dysfunction. HIF-1 acts as a cellular oxygen sensor, tuning the balance of metabolic and oxidative stress pathways to provide ATP and sustain cell survival. Acting on mitochondria, HIF-1 regulates different processes such as energy substrate utilization, oxidative phosphorylation and mitochondrial dynamics. In turn, mitochondrial homeostasis modifications impact HIF-1 activity. This underlies that HIF-1 and mitochondria are tightly interconnected to maintain cell homeostasis.

Despite many evidences linking HIF-1 and mitochondria, the mechanistic insights are far from being understood, particularly in the context of cardiac diseases. Here, we explore the current understanding of how HIF-1, reactive oxygen species and cell metabolism are interconnected, with a specific focus on mitochondrial function and dynamics. We also discuss the divergent roles of HIF in acute and chronic cardiac diseases in order to highlight that HIF-1, mitochondria and oxidative stress interaction deserves to be deeply investigated. While the strategies aiming at stabilizing HIF-1 have provided beneficial effects in acute ischemic injury, some deleterious effects were observed during prolonged HIF-1 activation.

Thus, deciphering the link between HIF-1 and mitochondria will help to optimize HIF-1 modulation and provide new therapeutic perspectives for the treatment of cardiovascular pathologies.

1. Introduction

Hypoxia, energy deprivation and mitochondrial dysfunction underlie the development of cardiac diseases such as acute ischemic injury or heart remodeling [1]. A decrease in dioxygen (O₂) levels, whether it is due to coronary artery occlusion, decreased tissue perfusion or sleep apnea, leads to hypoxia, which affects metabolism and function of the heart. The Hypoxia Inducible factor 1 (HIF-1) is recognized as the main transcription factor governing the adaptive response to hypoxia, as its regulation system is a key cellular O₂ sensor. HIF-1 target genes enables to accommodate the cell to O₂ deprivation through various mechanisms such as restoring O₂ delivery through angiogenesis and reducing O₂ consumption by shifting mitochondrial respiration to anaerobic glycolysis [2]. As such, the adaptive response mediated by HIF-1 is intricately linked to mitochondria, regulating oxidative phosphorylation, substrate utilization, oxidative stress and mitochondrial integrity. Mitochondria are organelles described as “energy factories”, whose functions depend on cell metabolism, substrate availability, O₂ supply and own integrity

preservation. Optimal mitochondrial O₂ consumption, reactive oxygen species (ROS) management and Adenosine Tri Phosphate (ATP) production is a trinomen that is tightly controlled by mitochondria and that impacts HIF-1 canonical and non-canonical regulations. Thus, HIF-1 and mitochondria are interconnected but their interplay has been mostly described in cancer cells [3]. In the context of ischemic cardiac diseases where O₂ and mitochondria homeostasis are particularly challenged, the mechanistic connexions between HIF-1 and mitochondria are far from being understood. From a pathophysiological point of view, myocardial ischemic diseases development and progression are characterized by functional and structural adaptations that can derive into maladaptation. In this context, HIF-1 has been demonstrated to impact on mitochondrial function and/or dynamics. Initially, stimulation of HIF-1 activity has been reported as a beneficial strategy to maintain mitochondrial homeostasis and to protect against cell death during ischemia. However, more recent studies indicate that prolonged activation of HIF-1 has opposite and deleterious consequences on ventricular remodeling and dysfunction. Thus, it appears very relevant to discuss

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the current understanding of the mechanisms of action of HIF-1 on reactive oxygen species (ROS) buffering and cell metabolism, with a particular emphasis on mitochondrial function and dynamics. By deciphering the interplay between HIF-1 and mitochondria in response to myocardial stress, HIF-1 modulation strategies could be optimized to improve therapeutic strategies in the field of cardiovascular diseases. In this review, we discuss the current knowledge on the “HIF-1-mitochondria” axis in order to highlight how a more specific targeting of HIF-1 activity has to be considered in different pathophysiological contexts.

2. The hypoxia inducible Factor-1 and mitochondria

2.1. The hypoxia inducible factor 1 (HIF-1)

HIF-1 belongs to the HIF family that is a key regulator of the cellular response to hypoxic stress. The HIF family is composed of four members: HIF-1 α , HIF-2 α , HIF-3 α and HIF-1 β (also called ARNT), which all contain a basic Helix Loop Helix domain (bHLH) - Per ARNT Sim homology domain (PAS), enabling heterodimerization and DNA binding (Fig. 1A). Members of the HIF family also contain N- and C-terminal transactivation domains (N-TAD or C-TAD) involved in transcriptional regulation. HIF-1 α and HIF-2 α contain both N-TAD and C-TAD whereas HIF-1 β contains only a C-TAD. The presence of a TAD in HIF-3 α is controversial depending on isoform and species concerned [4](Fig. 1A). HIF-1 is a heterodimer composed of the oxygen-sensitive α subunit and the constitutively expressed β subunit (Fig. 1B). The heterodimeric HIFs act as transcription factors triggering the expression of numerous genes involved in angiogenesis, growth, survival, glucose and lipid metabolism, inflammation ... [5]. HIF-1 was discovered in 1991, and its canonical regulation has been described within the following decade by Semenza, Kaelin and Ratcliffe who received the Nobel prize in 2019 [6]. At present, HIF-1 is the best-known member of the family and its role in cardioprotection and/or in chronic cardiac diseases has been extensively studied, although its mechanisms of action remain unclear [7].

Oxygen levels can affect the stability and subcellular localization of HIF-1 α while HIF-1 β is permanently localized in the nucleus (Fig. 1B). HIF-1 α is constitutively expressed but its half-life is approximately 5 min [8] and depends on the PO₂ and redox status of the cell. Indeed, HIF-1 α primary sequence contains an oxygen-dependent degradation domain (ODD) (Fig. 1A) with 2 proline residues (Pro 402/564 in humans) that are hydroxylated by prolyl-4-hydroxylases (PHDs) enzymes in normoxic condition. This leads to the recognition of HIF-1 α by the von Hippel-Lindau (VHL) protein, the recruitment of an E3-ubiquitin protein ligase complex, with subsequent ubiquitination and proteasomal degradation of HIF-1 α (Fig. 1B). In hypoxic conditions, PHDs are inhibited and HIF-1 α dimerizes with HIF-1 β to form HIF-1 that, in presence of a co-activator such as (CBP)/p300 (cAMP-Response-Element-Binding (CREB) Binding Protein), binds to Hypoxic Response Element (HREs) and activates gene transcription through the C-TAD [9] (Fig. 1A and B). The canonical regulation of HIF-1 also includes the factor inhibiting HIF-1 (FIH) that hydroxylates an asparagine residue (Asn 803 in humans) in order to block HIF-1 interaction with CBP/p300. This results in the inhibition of the transcriptional activity of the C-TAD domain of HIF-1 [10] (Fig. 1A and B).

A non-canonical regulation of HIF-1 activity has also been described. Among the mechanisms involved, some post-translational modifications of HIF-1 α were reported to alter HIF-1 α expression and interaction with VHL and CBP/p300, modulating its stability, localization and/or transactivation activity [11]. HIF-1 α can be phosphorylated and, depending on the phosphorylation site (i. e. PAS, N-TAD, C-TAD, ODD), this can modulate each step of the HIF-1 canonical pathway. For example, Akt signaling pathway has been shown to increase HIF-1 α synthesis through mammalian Target Of Rapamycin (mTOR) kinase [12, 13]. ERK-dependent phosphorylation of HIF-1 α affects its nuclear translocation and transactivation activity [14,15]. Depending on the PO₂ and the redox status of the cell, HIF-1 α acetylation at Lys674 can be modulated by the sirtuin 1 (Sirt1), which controls its interaction with CBP/p300 and consequently, its transcriptional activity [16]. Non-coding RNAs are also involved in HIF-1 α non canonical regulation.

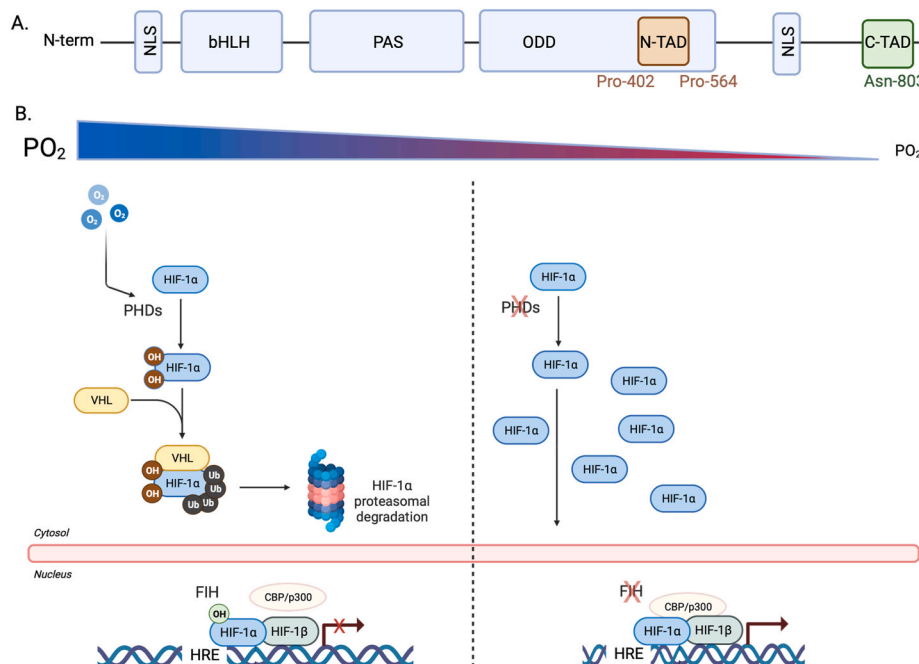


Fig. 1. Canonical regulation of Hypoxia Inducible Factor-1 (HIF-1). (A) Primary sequence of HIF-1 α and hydroxylation sites. NLS: nuclear Localization Sequence; bHLH: basic Helix Loop Helix domain, PAS: Per ARNT Sim homology domain; ODD: Oxygen-Dependent Degradation domain; N-TAD: N-terminal transactivation domain; C-TAD: C-terminal transactivation domain (B) Canonical regulation of HIF-1 activity. PO₂: partial pressure in O₂; PHDs: prolyl-4-hydroxylases; VHL: Von Hippel Lindau; Ub: ubiquitination; FIH: Factor Inhibiting HIF; CBP/p300: cAMP-Response-Element-Binding Protein; HRE: Hypoxia Responsive Element. Created with Biorender.com.

Some miRNAs can directly affect HIF-1 α expression as demonstrated by the down-regulatory effect of miR-33b on HIF-1 α expression in osteocarcinoma cells [17]. Indirectly, miR-198, known to decrease HIF-1 α expression, is inhibited by long non-coding RNAs (lncRNAs), leading to an increase in HIF-1 α content [18]. Some lncRNAs have been shown to modulate HIF-1 α expression and HIF-1 activity by different mechanisms including chromatin remodeling, post-transcriptional and post-translational modifications [19]. Interestingly, HIF-1 transcriptional activation leads to the transcription of genes encoding for molecules which are able to regulate its own activity [20]. Among them, during prolonged hypoxia, miR-155 has been identified to reduce HIF-1 α mRNA expression and HIF-1 activity in intestinal cells [21]. Another illustration is provided in glioblastoma cells in which hypoxia increases PHD2 and PHD3 expressions which are able to reduce HIF-1 α expression, even at low O₂ concentration [22]. Finally, even if HIF-1 α and HIF-2 α are structurally highly similar and can collaborate to respond appropriately to hypoxia, some studies reported that HIF-1 and HIF-2 can have opposite effect [20]. For instance, this was well illustrated in the context of PO₂ chemosensitivity of carotid bodies in response to hypoxia. Using HIF-1 α heterozygous mice, HIF-1 was demonstrated to be responsible for ROS generation and sympathetic over activation [23] whereas HIF-2 α was rather shown to maintain carotid body function through oxidative stress management (maintenance of pro/antioxidant enzymes activity) [24]. While HIF-1 impairs O₂-dependent chemosensitivity and induces oxidative stress in cerebral cortex from hypoxic mice [23]; HIF-2 is required to improve O₂-dependent chemosensitivity and increase anti-oxidant defenses in carotid bodies [24,25]. The most recently discovered member of the family is HIF-3. Apart from its role as an O₂-sensitive transcription factor partially sharing some target genes with HIF-1 and HIF-2, its ability to inhibit HIF-1 and HIF-2 activities has been demonstrated in renal carcinoma [26].

As a transcription factor that is finely regulated by a very complex O₂-sensitive system, HIF-1 plays a crucial role in shaping the metabolic and oxidative stress response during hypoxia, a process that is inextricably linked to mitochondria and that deserves to be more explored in the context of cardiovascular diseases.

2.2. Mitochondrial function and regulation in the heart

2.2.1. Mitochondrial function

Mitochondria are double-membrane organelles with an endosymbiotic origin that possess their own circular DNA and act as key regulators of cellular energetics. The respiratory chain located in the inner mitochondrial membrane (IMM) carries electrons from reduced Nicotinamide Adenine Dinucleotide (NADH) or reduced Flavine Adenine Dinucleotide (FADH₂) to O₂, generating a proton gradient necessary for the generation of ATP. The Tricarboxylic acid cycle (TCA) in the mitochondrial matrix allows for the generation of NADH and FADH₂ from nutrient metabolites to fuel the respiratory chain. Besides the production of ATP, mitochondria also control cellular levels of nucleotides and amino acids, and regulate the homeostasis of calcium (Ca²⁺) and iron [27,28]. Importantly, in addition to their role in cellular metabolism, mitochondria are now recognized as main determinants of cell fate by regulating death/survival, inflammation and senescence [29].

2.2.2. Mechanisms of maintenance of mitochondrial fitness

In response to environmental changes, the regulation of the above processes depends on mitochondrial fitness, which refers to their integrity, efficiency and dynamic response to stress. Mitochondrial fitness is maintained by quality control mechanisms including biogenesis, fusion, fission and mitochondrial autophagy (mitophagy). It represents a way to boost ATP production to meet metabolic demand under both physiological and pathological states. Mitochondrial biogenesis consists in the generation of new mitochondria through the concerted action of mitochondrial and nuclear genes [30]. It involves several steps

such as transcription of nuclear-encoded mitochondrial genes, mitochondrial translocation of the corresponding proteins, amplification of mtDNA and synthesis of mitochondrial phospholipids. Several transcription factors coordinate these actions with the peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1 α and PGC-1 β), the Nuclear respiratory factor 1 and 2 (Nrf1 and Nrf2) and the mitochondrial transcription factor A (TFAM), responsible for replication and transcription of mitochondrial DNA (mtDNA) [30].

Mitochondrial biogenesis is also influenced by the process of fission through the growth and division of pre-existing mitochondria. Indeed, mitochondria are highly dynamic organelles that change their morphology through multiple cycles of fission and fusion [31]. Mitochondrial fission generates small, spherical mitochondria, whereas fusion generates tubular or elongated mitochondria. The major proteins involved in mitochondrial dynamics are dynamin-like GTPases with dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1) regulating fission while optic atrophy 1 (Opa1) and mitofusins 1/2 (Mfn1/2) regulating the fusion. The process of fusion allows the mixing of macromolecules from damaged and intact mitochondria as a form of complementation in response to stress [32]. On the other hand, separating damaged organelles from the intact network by fission represents an important step to allow the degradation of mitochondria with lower membrane potential through mitochondrial autophagy (mitophagy) [33,34]. One mechanism of mitophagy is mediated by the protein PTEN induced kinase 1 (PINK1) that builds-up on the OMM of mitochondria with reduced membrane potential, leading to the recruitment of Parkin, an E3 ubiquitin ligase, and promoting the formation of ubiquitin chains. Ubiquitin chains are recognized by autophagy adaptors that bind to microtubule-associated protein 1A/1B-light chain 3 (LC3) proteins and target the cargo to autophagosomes, which are trafficked and degraded inside the lysosome [35]. Other pathways of mitophagy depend on the accumulation of mitophagy receptors on the OMM that directly bind to LC3 proteins. One family involves Bcl-2 interacting protein 3 (BNIP3) and BNIP3L (Nix), that participates in the hypoxic response, and the other group includes FUN14 domain containing protein 1 (FUNDC1) [36].

Mitophagy plays a key role in non-replicating cells such as cardiomyocytes that require efficient quality control mechanisms to replace or repair organelles in response to stress. In addition, in light of the importance of mitochondria to sustain cardiac metabolic needs, an imbalance in any of these mitochondrial dynamic processes will have deleterious consequences on cardiac function [37].

2.2.3. Consequences of impaired mitochondrial function

The heart is an important O₂ and nutrients consumer, accounting approximately a 40%-volume of mitochondria per cardiomyocyte [38]. To provide a constant supply of energy, cardiac cells display some substrate plasticity to accommodate the changes in the environment, such as O₂ and nutrient availability. Fatty acids are the preferred substrate in physiological conditions, accounting for 60–90 % of the myocardium's energy supply but ischemia is associated with an increased glucose utilization [27,39]. Disruption of mitochondrial homeostasis in situations of stress can lead to cardiomyocyte ATP depletion, reduced NAD⁺ pool and ROS accumulation with strong consequences on cell function and survival [40]. In addition, Ca²⁺ dysregulation exacerbates energy depletion and mitochondrial dysfunction [41].

Oxidative stress occurs as an imbalance between the production of ROS and their degradation by antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutase) or buffering systems such as glutathione or vitamins C and E [40]. Mitochondria are the main cellular source of oxidative stress and ROS are formed by the respiratory chain during oxidative phosphorylation. As electrons are transferred between the complexes, some of these electrons “leak” out and react directly with O₂ to form superoxide. Other sources of mitochondrial ROS in the heart are p66shc, NADPH oxidase (NOX4), and the monoamine oxidases that breakdown monoamines such as catecholamines and serotonin to

generate peroxide (H_2O_2) [42].

Protein and lipid oxidations result in decreased enzymatic activities that compromise the metabolic capacity of the mitochondria. Increased oxidative stress is also associated with mtDNA damage, impaired mitochondrial biogenesis and mitophagy [43]. The disruption of mitochondrial fitness further causes oxidative stress that form a vicious cycle driving cardiac damage progression. The mitochondrial permeability transition pore (mPTP) is sensitive to Ca^{2+} and/or ROS overload, which trigger its opening and the loss of mitochondrial membrane potential. This alters ATP production and leads to the release of mitochondrial proteins such as cytochrome *c*, an inductor of necrotic and apoptotic pathways [43]. In addition, mtDNA and/or ROS trigger the activation of the inflammasome leading to inflammation [44]. Mitochondrial oxidative stress is also well recognized as an important trigger of senescence [29].

Interestingly, in recent years, mitochondrial dysfunction and ROS have been identified as major consequences of hypoxic stress [45,46]. Indeed, in each cell, it exists a homeostasis set point where O_2 consumption, ATP production and ROS production are optimized to ensure cell function. For instance, during ischemia, a drop in PO_2 leads to a decrease in ATP production that can increase ROS production and lead to cell death, especially if anti-oxidant systems are overwhelmed [9] (Fig. 2A).

2.3. Interplay between HIF and mitochondria

2.3.1. Regulation of HIF-1 activity by the mitochondria

HIF-1 is the main transcription factor induced by hypoxia, which its “ O_2 -sensitive” subunit HIF-1 α being degraded in normoxic conditions while stabilized in hypoxic conditions. Therefore, its canonical regulation is completely dependent on O_2 homeostasis since PHDs enzymes are extremely reactive to PO_2 and need O_2 to add a hydroxyl group on the proline residues of HIF-1 α . However, the integrated hypoxic response

exhibits a more complex regulatory process because 1) PHDs also use α -ketoglutarate as a substrate and need Ferrous iron (Fe^{2+}) for full catalytic activity and; 2) mitochondrial ROS production and/or pro/anti-oxidant unbalance activates HIF-1 [46], Fig. 2B.

The PHD-dependent hydroxylation process is associated with the conversion of α -ketoglutarate to succinate, explaining why the accumulation of succinate and fumarate, which are TCA cycle metabolites, can have an inhibitory effect on PHDs activity [47], (Fig. 2B and C). As shown in tumor biopsies, a deficiency in enzymes allowing the transformation of succinate and fumarate (succinate dehydrogenase and fumarate hydratase) is accompanied by an increase in both metabolites, leading to PHDs inhibition and HIF-1 α stabilization [48]. Furthermore, since the functioning of the mitochondrial respiratory chain and the production of reduced elements (NADH, FADH₂) by the TCA cycle are tightly interconnected, any modulation of the oxidative phosphorylation activity will have consequences on TCA cycle metabolites accumulation, O_2 concentration, ROS production and subsequently PHDs activity. In prostate cancer cells, an impairment of the oxidative phosphorylation has been correlated to succinate accumulation and HIF-1 α stabilization [49]. On the other hand, by consuming O_2 , oxidative phosphorylation can induce hypoxia, leading to PHDs inhibition and HIF-1 α stabilization [50] (Fig. 2B and C). In line, mitochondrial biogenesis has been shown to increase both O_2 consumption and HIF-1 α expression in skeletal muscle cells [51]. These conflicting results highlight that the regulation of HIF-1 activity by oxidative phosphorylation is very complex. They also reveal the importance to consider O_2 homeostasis as a result of O_2 supply and demand at a local point in the cell, depending on the global environment (Fig. 2A). For instance, in cells exposed to hypoxia, an inhibition of the oxidative phosphorylation by nitric oxide has been associated with an increase in O_2 availability allowing O_2 to relocalize and activate other enzymes [50]. Among them, PHDs were identified, leading to a decrease in HIF-1 α levels even under hypoxia, explaining how the cells became unable to detect hypoxia [50]. Another example concerns the ability of

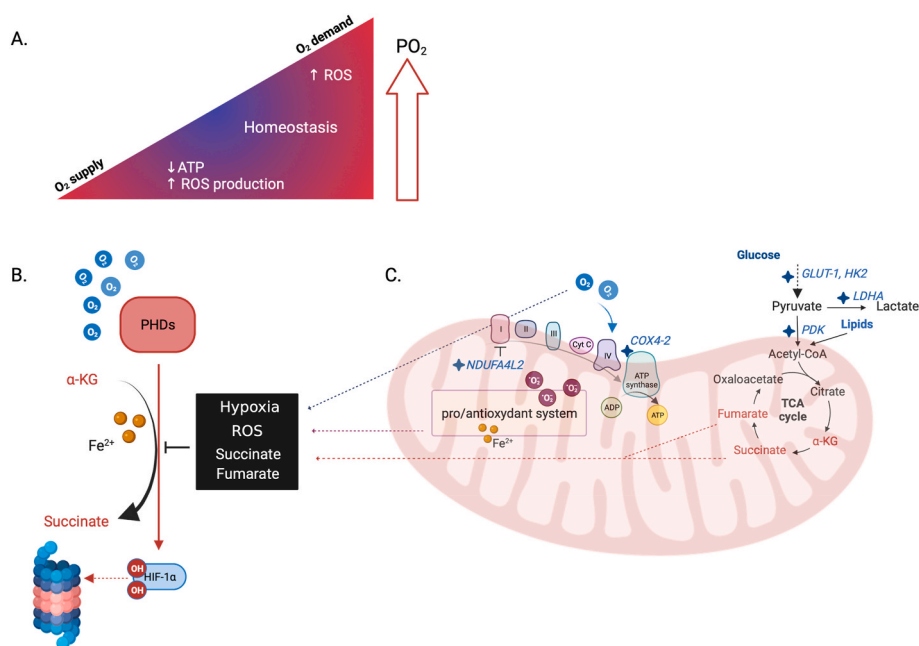


Fig. 2. Interplay between HIF-1 and mitochondria. (A) Oxygen (O_2) homeostasis is determined by cell environment, a balance between O_2 supply/demand and mitochondrial function at a local point. In each cell, a set point is established at which O_2 consumption, ATP production and ROS production and buffering are optimized to avoid cell death. (B) Regulation of HIF-1 α stabilization by prolyl-4-hydroxylases (PHDs). PHDs need O_2 , α -ketoglutarate (α -KG), ferrous iron (Fe^{2+}) to hydroxylate HIF-1 α ; PHD are inhibited by hypoxia, reactive oxygen species (ROS), succinate and fumarate which are all controlled by mitochondrial function (dotted arrows). (C) Regulation of mitochondrial function and ROS production by HIF-1 or regulation of mitochondrial fitness by HIF-1. Blue stars \star represent HIF-1 target genes which control mitochondrial fuel, tricarboxylic acid (TCA) cycle and respiration; Glucose Transporter-1 (GLUT-1), hexokinase 2 (HK2), pyruvate dehydrogenase kinase (PDK) and lactate dehydrogenase A (LDHA), cytochrome *c* oxidase sub-unit 4-2 (COX4-2), NADH dehydrogenase [ubiquinone] 1 alpha sub-complex, 4-like 2 (NDUFA4L2). Created with [Biorender.com](https://www.biorender.com).

ROS to inhibit PHDs. Under hypoxia, cells with a mutation in the complex 3 of the respiratory chain are incompetent for respiration but still generate H_2O_2 , that inhibit PHDs and lead to HIF-1 α stabilization [52]. This means that PHDs activity, and obviously HIF-1 α expression, is finely controlled by the pathophysiological state including the metabolic activity, the PO_2 level as well as the redox status of the cell.

Interestingly, Fe^{2+} is also required for PHDs catalytic activity by stimulating the α -ketoglutarate decarboxylation and transformation into succinate (Fig. 2B). This contributes to the formation of oxidized ferryl ($Fe^{3+/4+}$) that in turn, favors the hydroxylation process. Thus, the maintenance of Fe^{2+} redox status and iron homeostasis plays a pivotal role in HIF-1 α stabilization [47]. Furthermore, iron homeostasis is partially controlled at the mitochondrial level, since Fe^{2+} is mobilized in the Fenton reaction that produces hydroxyl radical (OH^\cdot) from H_2O_2 and lipid alkoxyl radicals from lipid peroxides. Of note, the antioxidant machinery of mitochondria allows to maintain iron homeostasis by limiting H_2O_2 production and transforming lipid peroxides into lipid alcohol, using SOD and GPX4, respectively [53]. In a wider context, ROS generation has been recognized to be a potent activator of HIF-1 (Fig. 2B and C). Indeed, especially in the context of intermittent hypoxia, where reoxygenation phases are frequent, mitochondrial superoxide anion production by NOX has been demonstrated to increase HIF-1 α stability through PHDs inhibition [54]. Then, superoxide anion formation has been shown to increase HIF-1 α transactivation activity and expression through Ca^{2+} -dependent mechanisms. On one hand, in pheochromocytoma cells, ROS production activates the Phospholipase C_γ , leading to inositol-3-phosphate production and intra-cytosolic Ca^{2+} overload. Calcium mobilization activates the Ca^{2+} -calmodulin kinase (CaMK) inducing the phosphorylation of p300, in order to reinforce HIF-1 transactivation [55]. On the other hand, the increase in cytosolic Ca^{2+} concentration activates the protein kinase C, that in turns phosphorylates the mTOR anabolic factor, leading to a rise in HIF-1 α synthesis [55].

Thus, considering mitochondria as a key player in regulating O_2 availability, mitochondrial homeostasis is crucial for HIF-1 regulation, underscoring that disruptions in mitochondrial fitness strongly impacts HIF-1 activity.

2.3.2. Regulation of mitochondrial fitness by HIF1

In turn, at the heart of the metabolic and redox status, HIF-1 is a key regulator of mitochondrial fitness. As a transcription factor, HIF-1 regulates the transcription of hundreds of targets, with a certain number of mitochondria-related genes [56]. Among them are genes involved directly (mitochondrial respiratory chain) or indirectly (glucose utilization and TCA cycle supply) [57] in mitochondrial function and in mitochondrial quality control (autophagy and mitophagy) [58]. Early studies demonstrated that HIF-1 regulated mitochondrial respiratory chain structure and oxidative phosphorylation efficiency. Under low O_2 availability, HIF-1 promotes the transcription of genes encoding for Lon protease and Cytochrome *c* oxidase subunit 4–2 (COX4-2) in order to optimize mitochondrial respiration by degrading COX4-1 (the most efficient mammalian cytochrome *c* oxidase 4–1) and replacing it by COX4-2 [59] (Fig. 2C). Actually, by switching Cox isoforms, HIF-1 is able to slow-down O_2 consumption and limit ROS generation [59,60]. Another mechanism consists in the stimulation of NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 4-like 2 gene transcription and expression by HIF-1 that inhibits complex I activity and limits ROS production [61] (Fig. 2C). HIF-1 is also considered as a main modulator of glycolysis and TCA cycle activity since it stimulates the transcription of genes encoding for the pyruvate dehydrogenase kinase (PDK) and lactate dehydrogenase A (LDHA), which favor anaerobic glycolysis. Indeed, PDK and LDHA drive the conversion of pyruvate to lactate instead of Acetyl CoA [62] (Fig. 2C). Combining with the role of HIF-1 in inducing transcription of genes encoding for rate limiting enzymes of glycolysis (i. e. hexokinase 2, phosphofructokinase ...), HIF-1 activity promotes anaerobic glycolysis to preserve O_2 consumption [57],

decrease ROS production and increase cell survival [62].

HIF-1 can also impact mitochondrial quality control mechanisms but here again, the effect of HIF-1 depends on the pathophysiological context and the tissue. The adaptation to hypoxia involves a reduction in mitochondrial mass to reduce O_2 consumption. In endothelial cells, HIF-1 α and HIF-2 α both contribute to decrease PGC1 β expression whereas solely HIF-2 α decreases TFAM expression [63]. Also, in skeletal muscle oxidative fiber, HIF-1 activity is associated with a decrease in respiratory chain complexes expression as well as a decrease in expression of transcription factors involved in mitochondrial biogenesis such as PGC-1 α , Nrf 1 and Nrf2 (Fig. 3). This is associated with an increase in glycolytic enzyme expression [64]. On the other hand, in mice myocardium, the drop in HIF-1 activity induced by birth is associated with an increase in mitochondrial biogenesis characterized by an increase in mtDNA/DNA ratio, citrate synthase activity and PGC1 α expression [65].

Indirectly, HIF-1 is overexpressed simultaneously with proteins that control mitochondrial fission and fusion [58]. There are evidences that hypoxia-mediated mitochondrial fission occurs through Drp1 phosphorylation [66,67] and/or Drp1 transcriptional activation [67] that is dependent on the activation of HIF-1 (Fig. 3). Hypoxia and HIF-1 are also recognized as positive regulators of mitophagy. HIF-1 is directly involved in regulating mitochondrial autophagy by the activation of BNIP3/NIX mitophagy receptors, allowing the elimination of oxidized mitochondria [67,68] (Fig. 3). A complementary signaling pathway involving another mitophagy receptor, FUNDC1, has been uncovered during hypoxia with boosted mitophagy that is dependent on HIF-1 [69] (Fig. 3). Finally, HIF-1 α has also been recently shown to be a positive regulator of parkin-mediated mitophagy in different pathological contexts such as acute kidney injury or in diabetes-associated complications [70–72].

3. Acute and chronic cardiac diseases

In several pathophysiological situations, the heart is subjected to hypoxia during which myocardial HIF-1 α would be expected to be stabilized. Such conditions include acute ischemia-reperfusion (I/R) injury, where ischemia is characterized by the obstruction of the blood flow leading to decreased O_2 and nutrients supply and reperfusion by a massive supply in O_2 and nutrients; cardioprotective strategies characterized by repetitive episodes of ischemia or hypoxia; or chronic cardiopathies described as a progressive process, starting from functional and structural adaptations (i. e. cardiac remodeling) to a maladaptive situation (i. e. heart failure).

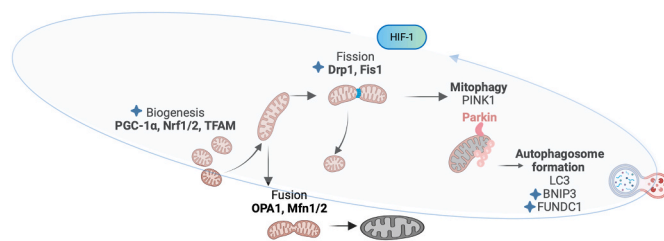


Fig. 3. Regulation of mitochondrial dynamics by HIF-1. Blue stars \star represent HIF-1 target genes which alters mitochondrial dynamics by controlling biogenesis, fission and mitophagy; peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1 α and PGC-1 β), the Nuclear respiratory factor 1 and 2 (Nrf1 and Nrf2) and mitochondrial transcription factor A (TFAM), dynamin-related protein 1 (Drp1), mitochondrial fission protein 1 (Fis1), optic atrophy 1 (Opa1), mitofusins 1/2 (Mfn1/2), PTEN induced kinase 1 (PINK1), microtubule-associated protein 1A/1B-light chain 3 (LC3), Bcl-2 interacting protein 3 (BNIP3), FUN14 Domain Containing 1 (FUNDC1). Created with [BioRender.com](https://www.biorender.com).

3.1. HIF-1 and cardioprotection

Myocardial infarction (MI) is characterized by a phase of ischemia that induces irreversible cardiomyocytes death and a phase of reperfusion that is characterized by different reversible damages such as stunning and hibernation, as well as irreversible cardiomyocytes death [73]. Both stunning and hibernating situations lead to a decrease in myocardial function but the two processes are related to distinct mechanisms. Stunning involves ROS production as well as Ca^{2+} homeostasis and excitation-contraction coupling, without having any impact on ATP production. On the other hand, hibernation is tightly related to the mitochondria and aims at slowing metabolic function in order to protect the heart against post-MI ventricular dysfunction and structural alterations. Hibernation is thus a process that can confer cardioprotection. Here, we will focus on cell death and infarct size during I/R and MI, because infarct size is a major determinant of long term post-MI recoveries [74]. In human biopsies, myocardial HIF-1 α mRNA content is increased in response to MI, providing arguments to explore HIF-1 signalization during and/or after MI [75]. Besides, one of the most frequent contexts in which HIF-1 has been shown to participate in the response to I/R is the field of cardioprotective strategies. The first pre-clinical study showing HIF-1 α as a mediator of cardioprotection demonstrated that the injection of HIF-1 α plasmid DNA into the infarcted area, limited infarct size by increasing capillary density and myocardial blood flow, thus improving O_2 and nutrients supply [76]. Although attempts to activate HIF-1 have not always been successful, some studies have achieved to identify HIF-1-dependent key mechanisms of cardioprotection. For instance, HIF-1 is well-recognized to activate the transcription of genes encoding for proteins which enhance coronary perfusion such as vascular endothelial growth factor (VEGF), erythropoietin (EPO) and Heme Oxygenase-1 [77]. However, in this review, we will focus on the impact of HIF-1 on mitochondrial function and dynamics.

Initially, HIF-1 has been investigated in the context of ischemic preconditioning, consisting in the application of several short ischemic stress before the sublethal I/R. Especially HIF-1 has been supposed to mediate the second window of cardioprotection [78] that appears 12–24 h after the preconditioning but, more recent studies indicate that HIF-1 is also involved in the acute phase of cardioprotection (2–4 h) [79]. HIF-1 also participates in postconditioning, which consists in short ischemic stress applied at the onset of reperfusion [78]. In all of these situations, HIF-1 appears to preserve mitochondrial function and structure. One of the main mechanisms recognized to induce cardioprotection is a moderate production of ROS, activating several protective pathways such as the Survivor Activating Factor Enhancement (SAFE) and the Reperfusion Injury Salvage Kinase (RISK) pathways. SAFE and RISK both converge on mitochondria in order to prevent the opening of mitochondrial ATP-sensitive potassium channel (mK_{ATP}) and mitochondrial permeability transition pore (mPTP) [80]. In 2008, Cai et al. demonstrated that HIF-1 α is required to decrease infarct size following ischemic preconditioning, through mitochondrial ROS production [81]. Indeed, in isolated perfused heart, using HIF-1 α heterozygous mice, they demonstrated that ischemic preconditioning required HIF-1 to increase mitochondrial ROS production and inhibit PTEN that maintained Akt phosphorylation and triggered cardioprotection [81]. In PHD2 hypomorph mice expressing a low amount of PHDs, the stabilization of HIF-1 α is associated with a “hibernating state”. Indeed, HIF-1 increased mRNA and protein expressions of genes involved in glycolysis such as Glucose Transporter-1 (GLUT-1) and PDK-1, leading to the preservation of ATP production after ischemia and to a higher phospho-creatine/creatine ratio, indicating a higher energy metabolic status [82]. The sustained level of ATP production maintained the mK_{ATP} channel closed, avoiding Na^+ and Ca^{2+} overload and preventing functional alterations. In agreement with the role of HIF-1 in inducing anaerobic glycolysis, mice lacking PHDs also displayed a higher content of lactate before ischemia, that could be assimilated to a preconditioning

state, allowing to maintain the mPTP closed and to prevent cardiomyocytes death [82]. In agreement, Ong et al. demonstrated that pharmacological inhibition of PHDs induced HIF-1-dependent increase in HK2 expression, to enhance anaerobic glycolysis, decrease mitochondrial ROS overproduction and delay mPTP opening at reperfusion [83]. The beneficial impact of HIF-1 stabilization on massive ROS production, mPTP opening and cardiomyocytes viability is also demonstrated in mice lacking VHL [83]. In addition, the activation of HIF-1 by I/R improved cardiomyocyte viability by preserving mitochondrial integrity and decreasing mitochondrial ROS through the transcription of the gene encoding frataxin, an iron chelator [84]. More recently, HIF-1-induced cardioprotection has been related to its ability to induce autophagy. In cardiomyoblasts, activation of HIF-1 α by hypoxia increased autophagosome formation, characterized by an increase in Beclin-1, LC3II/I ratio, Atg5 and Atg7 expressions, and preserved cell viability [85]. The beneficial effect of HIF-1 α stabilization on autophagy has also been demonstrated in sevoflurane-postconditioned rats [81,86]. Indeed, sevoflurane increased HIF-1 α , Beclin-1 and LC3II/I expressions. However, in diabetic rats where HIF-1 α expression is decreased, the addition of deferoxamine, a Fe^{2+} chelator, is required to inhibit PHDs and restore HIF-1 α content. The reactivation of HIF-1 in diabetic rats increased autophagy levels and reduced infarct size that is accompanied by a drop in ROS production and an increase in ATP production [86]. In rats, the stabilization of HIF-1 α by dimethylxalylglycine (DMOG), an α -ketoglutarate analog that inhibits PHDs, stimulated autophagy through BNIP3 and decreased infarct size [87].

3.2. HIF-1 and chronic cardiomyopathies

Chronic ischemia or increased mechanical load are two major leading causes of heart failure. Interestingly, HIF-1 α expression is increased in mouse models of cardiac hypertrophy [88,89] and in the myocardium of patients with ischemic heart disease, which suggests an important role in cardiac adaptation to chronic stress [75]. In addition, HIF-1 α is also upregulated in cardiomyocytes stimulated with hypertrophic agents [88].

In order to better understand the role of HIF-1 in the onset of cardiomyopathies, transgenic approaches have been used to delete or force the expression of HIF-1 in the heart of mice. Global deletion of HIF-1 α or HIF-1 β resulted in embryonic lethality with severe cardiac malformations, which prompted the development of conditional tissue-specific approaches [90,91]. Deletion of HIF-1 α in cardiomyocytes is not accompanied by embryonic lethality but adult mice displayed spontaneously cardiac contractility and relaxation impairment [92]. This is due to defective cardiac vascularization but also to an intrinsic impairment in cardiomyocyte contractility. Gene expression measurements revealed a downregulation of the angiogenesis pathway (VEGF), the calcium Sarco/Endoplasmic Reticulum Calcium-ATPase 2 (SERCA2) and glucose metabolism pathway (Glut1, LDHA, phosphoglycerate kinase), the latter being confirmed by impaired ventricular glucose utilization and ATP production [92]. Thus, HIF-1 α appears necessary to sustain cardiac contractility and metabolic gene expression in the heart at baseline. On the other hand, while constitutive expression of HIF-1 α in transgenic mice is well tolerated in young adults that were characterized by enhanced vascularization, increased glycolysis and increased calcium transients, these mice developed heart failure in the long term [93]. This indicates that, although short-term activation of HIF-1 is beneficial, prolonged activation of HIF-1 over time drives the development of cardiomyopathy [93]. This is also exemplified in mice that overexpress an O_2 -insensitive form of HIF-1 α in the heart. In this model, the deleterious effects of HIF-1 α occurred rapidly with the development of ventricular dysfunction, accompanied by an upregulation of glycolytic genes and an altered expression of calcium-related genes [94]. Alternatively, forced expression of HIF-1 α was achieved in cardiomyocytes through targeted-deletion of VHL or PHD2/PHD3, which led to reprogramming of angiogenesis and metabolism, cardiomyocyte

death and heart failure [88,95]. These latter studies confirmed that chronic and dysregulated activation of HIF-1 α at baseline precipitates ventricular dysfunction.

These different genetically-modified mouse models were also useful for evaluating the role of HIF-1 during chronic cardiac stress. In a model of pressure overload or chronic ischemia, cardiac-specific overexpression of HIF-1 α or inactivation of PHD2 aggravated the development of HF [93,95]. On the other hand, Krishnan et al. demonstrated that cardiac-specific deletion of HIF-1 α prevented hypertrophy and contractile dysfunction during pressure overload or isoprenaline infusion [88]. Interestingly, they found that HIF-1 α overactivation is responsible for myocardial toxic triglycerides accumulation through direct activation of PPAR γ and metabolic reprogramming of genes involved in glycolysis and lipid handling [88]. They also made a direct link between HIF-1 α activation, decreased mitochondrial respiration and decreased mtDNA content in the heart [88]. Moslehi et al. also further provided evidences that some of the deleterious effects of chronic activation of HIF-1 were due to excessive glucose and fatty acid uptake, leading to an accumulation of glycogen and lipids in the heart [95]. Interestingly, they also observed an accumulation of abnormal mitochondria in the heart, with decreased O $_2$ consumption and decreased mtDNA levels. However, they showed no evidences for mitochondrial biogenesis alterations since PGC-1 α and PGC-1 β are unaltered, but instead BNIP3 was increased, indicating putative enhancement of mitophagy [95].

Alternatively, transient HIF-1 α stabilization through pharmacological approaches designed to inhibit PHDs has demonstrated improvement in post-MI ventricular remodeling with reduction of myocardial fibrosis and inflammation [96,97]. However, in this case, HIF-1 may not be the sole driver of anti-fibrotic effect since PHDs are also essential for collagen formation. Indeed, post-MI functional and post-MI recoveries have been reduced and associated with a decrease in collagen synthesis in mice treated with a small PHD inhibitor [98].

3.3. HIF-1 and intermittent-hypoxia-related cardiomyopathies

Intermittent Hypoxia (IH) is defined as repetitive short cycles (1 min–10 min) of O $_2$ saturation-desaturation. When applied chronically (several hours, several consecutive days), IH is used to evaluate the consequences of the obstructive sleep apnea syndrome (OSAS). OSAS affects 1 billion people in the world and is recognized as an independent risk factor for cardiovascular diseases [99,100]. Especially, it is associated with an increased risk of MI, a higher infarct size and less post-MI recoveries compared to non-apneic patients [101]. In this context, animal models of IH were developed and a recent meta-analysis performed in rodents demonstrated that acute (few hours) application of moderate normobaric IH (PO $_2$ 10 %) decreased infarct size whereas chronic (several days) application of severe normobaric IH (PO $_2$ 5 %) increased infarct size [102]. Interestingly, IH is a stimulus that sustainedly activates HIF-1. Indeed, Yuan et al. demonstrated that both continuous and intermittent hypoxia increased HIF-1 α levels in PC12 cells. However, HIF-1 α expression rapidly decreased upon reoxygenation in cells exposed to continuous hypoxia, while HIF-1 α expression was still high upon reoxygenation in cells that were exposed to IH [54]. One explanation is that IH is a potent ROS generator [103] that induces prolonged HIF-1 α stabilization and HIF-1 activation through Ca $^{2+}$ and mTOR-dependent pathways and PHDs inhibition, as previously described [2,45]. Therefore, the consequences of HIF-1 activation under IH are highly dependent on the duration and the severity of the stimulus. In both acute/moderate or chronic/severe IH, HIF-1 is activated and triggers different signaling pathways contributing either to beneficial or deleterious effects. In the following section, by reporting studies also using HIF-1 $\alpha^{+/-}$ mice, we aim at illustrating that the ambivalent response to I/R depends on the hypoxic pattern (effects of several days of IH exposure to compare with effects of ischemic pre/post-conditioning consisting in short repetitive episodes of hypoxia as described above).

The deleterious effects of chronic IH were mainly illustrated in the context of IH-mimicking OSAS. Indeed, myocardial HIF-1 α expression was correlated with the severity of OSAS in patients at high cardiovascular risk [104]. In rats, chronic exposure to IH activated HIF-1 that participated in coronary flow alteration and cardiomyocyte death after I/R [105]. The involvement of HIF-1 in IH-induced cardiomyocyte death was confirmed in HIF-1 $\alpha^{+/-}$ mice exposed to chronic (8 h a day, 14 days) and severe (60min cycle of FiO $_2$ 21%-FiO $_2$ 5 %) IH, which were protected against I/R, compared to HIF-1 $\alpha^{+/+}$ mice [106]. Even if the impact of HIF-1 on mitochondrial function or dynamics is poorly documented in the context of cardiac diseases, some studies reported a crosstalk between HIF-1 and mitochondria under chronic IH. For instance, chronic IH increased CaMKII and HIF-1 α expressions as well as mitochondria-dependent apoptotic factors release [107]. Using HIF-1 $\alpha^{+/-}$ mice, several mechanisms related to mitochondria were proposed to explain how IH induces HIF-1-dependent cardiomyocytes death. Under HIF-1 control, IH increased oxidative stress as characterized by an accumulation of superoxide anion [103]. IH also induced ER stress and cardiomyocyte apoptosis [104]. In agreement with IH-induced oxidative and ER stress, Moulin et al. also demonstrated that IH decreased mitochondrial O $_2$ consumption. This was associated with a disruption of the mitochondria-associated ER-membranes, whose integrity is essential to maintain ER, mitochondrial function and Ca $^{2+}$ homeostasis [108]. In line, PHD3 overexpression decreased HIF-1 α and stabilized the level of SERCA2, contributing to maintain Ca $^{2+}$ homeostasis and to reduce IH-induced myocardial dysfunction in mice [109].

4. Conclusion and future perspectives

HIF-1 acts as a cellular oxygen sensor that modulate metabolic pathways to provide ATP, ensure ROS buffering and drive cell survival in situations of oxygen deprivation. As such, HIF-1 has been shown to regulate mitochondrial respiration and mitochondrial quality control in different tissues. At present, there is a paucity of knowledge on the mechanisms linking HIF-1 activation to mitochondria in the context of cardiac diseases. While HIF-1 α stabilization has demonstrated clear beneficial effects in acute ischemic injury, its chronic activation seems to induce cardiac remodeling and cardiomyocyte death on the long term. Although few studies have provided mechanistic insights on the deleterious effects of HIF-1 activation in the heart, mitochondria seemed to be particularly at play. These effects were associated with profound metabolic reprogramming (lipid and glycogen accumulation) and mitochondrial dysregulation through the alteration of pathways involved in biogenesis, fission and mitophagy [88,95]. Sustained HIF-1 activity is also responsible for the expression of genes encoding proteins involved in vascular and cardiac remodeling and ventricular dysfunction [92]. Finally, HIF-1 long-term activity induces Ca $^{2+}$ homeostasis alterations, ER stress and mitochondrial dysfunction, all of these mechanisms being related to cardiomyocytes death [104,108].

HIF-targeted therapies have been designed to inhibit PHDs and stabilize HIF-1 α in acute cardiac ischemic diseases. Among them, we find specific and non-specific strategies such as genetic overexpression of HIF-1 α , genetic ablation of PHDs or VHL and, pharmacological inhibition of PHDs through the chelation of Fe $^{2+}$ (deferoxamine) or through the analogic action of α -ketoglutarate (DMOG) [78]. In pre-clinical studies, these approaches have proven to be successful by increasing oxygen supply and optimizing oxygen utilization through angiogenesis, oxidative stress buffering, heme oxidation, RISK & SAVE pathways activation, hibernation mimesis and subsequent mitochondrial preservation. Several clinical trials were conducted in order to prove the beneficial effects of HIF-1 activation, especially through the transcription of the gene encoding for EPO [110]. Consequently, Roxadustat has been approved by the European Medicines Agency's in 2021 and Daprodustat has been approved by the FDA in 2023 in order to improve O $_2$ supply in anemic patients with chronic kidney diseases [111,112]. Despite the pre-clinical studies highlighting the beneficial effects

afforded by HIF-1 in terms of infarct size limitation and long-term post-MI recoveries, accumulating evidence suggests that long-term and sustained stabilization of myocardial HIF-1 α may be detrimental. Interestingly, strategies that aim at inhibiting HIF-1 activity have also been developed. They act directly or indirectly at different levels of HIF-1 α stabilization and activation and were developed and tested in clinical trials in order to counter the metastatic process (i.e. proliferation, angiogenesis, immunomodulation ...) [110]. For instance, Rapamycin, which indirectly decreases HIF-1 α translation and Vorinostat, that reduces its stability and its nuclear localization, have been approved by the FDA for the treatment of renal carcinoma and lymphoma, respectively [113]. These studies could be a great opportunity to deeply explore and correlate the impact of HIF-1 activation on mitochondrial function and dynamics with clinical cardiovascular outputs.

To conclude, HIF-1 appears to be a promising target in cardiac diseases but HIF-1 activity deciphers paradoxical effects that should be anticipated before the administration of the appropriate treatment. Indeed, depending on the pathophysiological context, HIF-1 is beneficial or deleterious for the cardiovascular system, meaning that its modulation should be individualized. This highlights the importance of studying how HIF-1 switches from adaptive to maladaptive effect in myocardium by 1) deeply investigating the multiple regulating system of HIF-1 (i. e. post-translational modifications, FIH, HIF-2 ...) and 2) more specifically focusing on the interplay between HIF-1, oxidative stress and mitochondria. This would ultimately need to specify the position of already existing HIF-1 modulators and/or to develop new HIF-1 specific inhibitors.

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CRediT authorship contribution statement

Jeanne Mialet-Perez: Writing – review & editing, Writing – original draft, Conceptualization. **Elise Belaidi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

None.

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