J Atheroscler Thromb, 2017; 24: 884-894.
http://doi.org/10.5551/jat.RV17009

Review

The Roles of Hypoxia Signaling in the Pathogenesis of Cardiovascular Diseases

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The circulatory system distributes blood flow to each tissue and transports oxygen and nutrients. Peripheral circulation is required to maintain the physiological function in each tissue. Disturbance of circulation, therefore, decreases oxygen delivery, leading to tissue hypoxia which takes place in several cardiovascular disorders including atherosclerosis, pulmonary arterial hypertension and heart failure. While tissue hypoxia can be induced because of cardiovascular disorders, hypoxia signaling itself has a potential to modulate tissue remodeling processes or the severity of the cardiovascular disorders. Hypoxia inducible factor-1α (HIF-1α) and HIF-2α belongs to a group of transcription factors which mediate most of the cellular responses to hypoxia at a transcriptional level. We, and others, have reported that HIF-α signaling plays a critical role in the initiation or the regulation of inflammation. HIF-α signaling contributes to the tissue remodeling processes; thus it has a potential to become a therapeutic target. Elucidation of the molecular link, therefore, between hypoxia signaling and tissue remodeling will greatly help us to understand the pathophysiology of the cardiovascular disorders. The purpose of this review is to give a brief overview of the current understanding about the function HIF-α in inflammation processes especially by focusing on its roles in macrophages. In addition, the pathophysiological roles of hypoxia signaling for the development of cardiovascular disease will be discussed.

Key words: Cardiovascular diseases, Inflammation, Hypoxia, HIF-1α

Introduction

While molecular oxygen is required to maintain the homeostasis in each cell, the oxygen consumption rate greatly varies depending on each tissue. For instance, the brain consumes approximately 3 ml O_2/min/100g tissue. The oxygen consumption rate in the heart is even larger at a rate of 8–15 ml O_2/min/100g tissue. It should be noted that it could rise up to 70 ml O_2/min/100g during vigorous exercise period[1, 2]. In general, the oxygen concentration below the tissue-specific physiological level is called hypoxia.

In the hypoxic environment, each cell exhibits several types of responses at transcriptional, translational or post-translational levels. Most of the gene expressions are, at the transcriptional level, significantly suppressed in the hypoxic environment. In contrast, the expression of a group of genes is significantly enhanced in hypoxia. These genes are termed as hypoxia-inducible genes. Representatives of hypoxia-inducible genes are genes related to angiogenesis (vascular endothelial growth factor-a, Vegf-a)[3], erythropoiesis (erythropoietin, Epo)[4], cellular metabolism (pyruvate dehydrogenase kinase, isoform 1, Pdk 1, or lactate dehydrogenase-a, Ldh-a)[5, 6] and inflammation (inducible nitric oxide synthase, iNOS)[7]. Hypoxia-inducible factor-1α (HIF-1α) and HIF-2α act as transcriptional mediators in their hypoxic induction[8, 9]. The activity of HIF-α is regulated at a post-translational level. In normoxic conditions, HIF-α protein is hydroxylated through an oxygen dependent process, and is degraded through a ubiquitin-proteasome system[10]. In contrast, the HIF-α protein is stabilized in

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Received: June 17, 2017
Accepted for publication: June 22, 2017

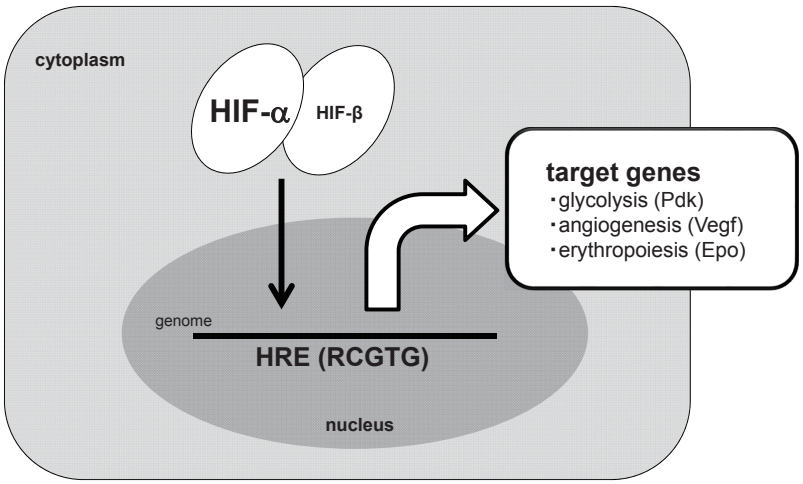

Fig. 1. HIF-α mediated cellular responses to hypoxia

In a hypoxia environment, HIF-α protein is stabilized and binds to the hypoxia responsive element (HREs) of each target gene, including glucose metabolism (Pyruvate dehydrogenase kinase (Pdk)), angiogenesis (Vascular endothelial growth factor-a (Vegf-a)) and erythropoiesis (Erythropoietin (Epo)).

hypoxic condition and translocated into the nucleus. After forming a heterodimer complex with HIF-1β, HIF-α binds to the hypoxia responsive elements (HRE) with a core consensus sequence (RCGTG), and activates the transcription of hypoxia-inducible genes[11, 12] (**Fig. 1**).

Sterile Inflammation in Cardiovascular Diseases

Most basic or clinical researches support the notion that an inflammatory process underlies the development of atherosclerotic processes. Monocytes are recruited in the subendothelial space of the arterial wall and differentiate into macrophage at the initial phase of atherosclerosis. Repeated innate immune responses, in turn, promote the deposition of lipid-loaded macrophages or foam cells, which secrete pro-inflammatory mediators and result in plaque destabilization[13, 14]. Consistent with these findings, the serum levels of inflammatory markers, including Creactive protein (CRP) and interleukin-6 (IL-6), are elevated in atherosclerotic patients[15-17].

The inflammatory process also contributes to the development of vascular remodeling in systemic hypertension or pulmonary artery hypertension (PAH)[18, 19]. An elevated serum level of CRP precedes the new onset of systemic hypertension in an elderly healthy population[20, 21]. Similarly, serum level of pro-inflammatory cytokines including interleukin 6 (IL-6) is elevated in PAH patients, and the cytokine abundance has a significant impact on the subsequent prognosis of PAH patients[22-24].

Heart failure is a condition in which the heart can't pump enough amount of blood to meet the body's needs. Heart failure with reduced ejection fraction (HFrEF; also known as systolic heart failure) develops after myocardial infarction or as one of the manifestation of cardiomyopathy. In contrast, heart failure with preserved ejection fraction (HFpEF) occurs in patients with systemic hypertension. It should be noted that the serum levels of inflammatory markers are increased in both HFrEF and HFpEF patients[25-27]. Importantly, the serum levels of CRP, IL-6 and tumor necrosis factor alpha (TNF-α) are associated with their prognosis[28-33].

These observations clearly indicate that an inflammatory signal plays a critical role during the processes of cardiovascular remodeling. It still remains unclear, however, why sterile inflammation develops in the vessel wall or in the cardiac tissue. Moreover, it should also be elucidated whether these inflammatory processes play an adaptive or mal-adaptive function.

HIF-α Switching in M1 / M2 Macrophage

Previously, it has been formerly considered that macrophages consist of a single cell population, and simply activate inflammatory processes in response to the tissue injury or infection[34]. A number of recent studies have revealed clearly that macrophages are composed of heterogeneous cell populations. Currently, several types of classification exist in defining each macrophage population based on its origin, loca-

tion or the function. Tissue macrophages may exist as a resident macrophage or may differentiate from monocyte populations[19]. One macrophage population activates inflammation (pro-inflammatory), but the other suppresses or resolves the inflammatory processes (anti-inflammatory)[35-37]. A number of definitions still exist regarding the pro- or anti-inflammatory macrophage population. Among them, it has been widely used for easy understanding of macrophage heterogeneity including M1 (pro-inflammatory) and M2 polarization (anti-inflammatory).

In *in vitro* experiments, M1 is usually induced by a combination of Th1 cytokine, interferon-γ (IFN-γ) and a ligand for toll-like receptor 4, lipopolysaccharide (LPS). IFN-γ and LPS robustly induce the expression of pro-inflammatory genes including *inducible nitric oxide* (*NO*) *synthase* (*iNOS*), and elicit the production NO. NO is one of the critical mediators in inflammation. Thus, the iNOS gene is considered as a classical M1 marker gene. On the other hand, M2 macrophage is induced by Th2 cytokines such as interleukin-4 (IL-4) or IL-13. Arginase 1 (Arg1) or the mannose receptor expression is highly expressed in M2 macrophages, thus these genes are known as M2 marker genes[38].

It should be noted that both iNOS and ARG1 enzymes catalyze and compete for the same metabolic substrate, *l*-arginine. While iNOS in M1 macrophage produces NO from l-arginine and strikingly promotes the inflammatory processes, ARG1 in M2 macrophage suppresses NO production[39]. The antagonistic activity, therefore, between iNOS and Arg1 crucially regulates the production of NO.

The roles of HIF-1α in M1 macrophage activation have been extensively investigated. LPS or IFN-γ mediated HIF-1α induction is required for iNOS gene expression in M1 macrophages[7, 40, 41]. In agreement with this, the severity of septic shock was significantly attenuated in myeloid-specific HIF-1α deficient (LysM-cre;HIF-1α$^{fl/fl}$) mice[42, 43]. Moreover, chemically induced cutaneous inflammation or experimental arthritis was also attenuated in HIF-1α deficient mice[44]. These results indicate that HIF-1α plays a critical role in M1 macrophage activation.

In contrast to the pro-inflammatory processes those are activated in M1 macrophages, little is known about its resolution process. We examined the expression of HIF-1α and HIF-2α in murine macrophages, and found that HIF-1α and HIF-2α are specifically expressed in M1 and M2 macrophages, respectively[43]. While LPS or IFN-γ significantly upregulated HIF-1α protein abundance, LPS and IFN-γ strikingly suppressed HIF-2α gene expression. In contrast, IL-4 or IL-13 significantly increased HIF-2α protein abundance in hypoxia. Importantly, we revealed that HIF-2α induces Arg1 gene expression in M2 macrophages. While both iNOS and Arg1 gene expression increase in hypoxia, iNOS and Arg1 utilizes distinct isoform of HIF-α in its hypoxic induction. Through a loss-of-function approach, we identified that HIF-1α potentiates, but HIF-2α suppresses NO production *in vivo*. These results revealed that the balance between HIF-1α and HIF-2α, named as HIF-α switching, critically determine the on/off regulation of NO production (**Fig. 2**).

The Role of Active Glycolysis in Macrophage Migration

In addition to its activation, migration is another important function of macrophages initiating inflammation[42, 45]. The processes of cell migration consist of a series of dynamic remodeling in actin cytoskeleton. While lamellipodia is an actin projection on the leading edge of the migrating cell, filopodia is a slender projection that extends beyond the lamellipodia[46]. During cell migration, dynamic recycling of actin polymerization and depolymerization takes place through an ATP dependent manner. It should be noted, therefore, that the cell migration process consumes abundant ATP in the cytosol[47, 48].

ATP can be synthesized through at least two metabolic pathways, including glycolysis in the cytoplasm and tricarboxylic cycle (TCA cycle) in the mitochondria. In glycolysis, two molecules of ATP are synthesized from one glucose molecule, accompanying the generation of lactate. Glucose can also be metabolized through a TCA cycle in the mitochondria via oxidative phosphorylation. Mitochondrial electron transport chain produces 36 molecules of ATP from glucose through an oxygen dependent manner.

While the oxygen concentration inside the blood vessel remains high, its concentration is strikingly decreased in the inflammatory area[49]. During the migration processes of monocyte derived macrophages, the oxygen concentration gradually decreases as macrophages migrate from the blood stream into the inflammatory area. It has been also well documented that mitochondrial activity is significantly suppressed in hypoxic condition, which is termed as the Pasteur effect or classic glycolysis[50]. ATP production in hypoxic condition should also be decreased. Given that macrophage migration consumes abundant ATP, how is it that macrophage can migrate under hypoxic environment?

We initially investigated which energy substrate is required for macrophage migration in hypoxia. Using Boyden chamber assay, we identified that glu-

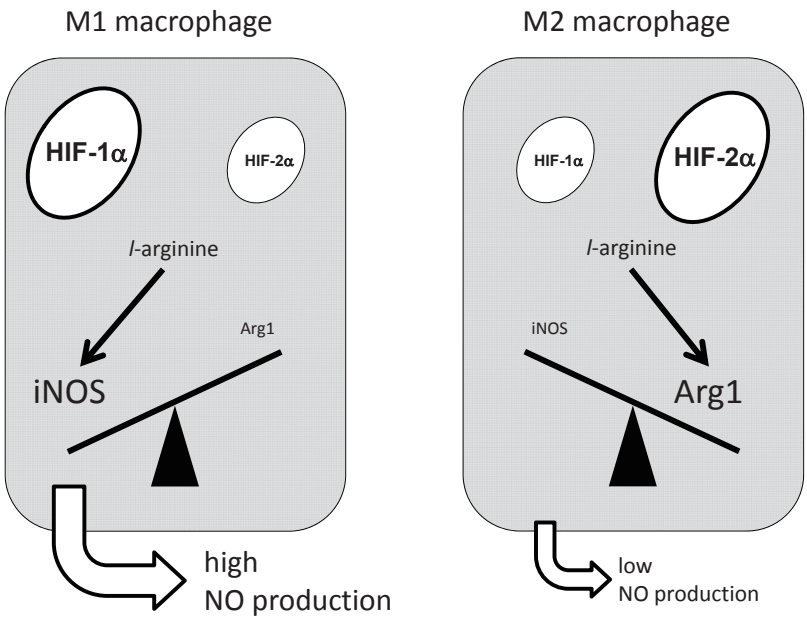

Fig. 2. HIF-α switching regulates nitric oxide (NO) production from macrophages.

HIF-1α activates iNOS gene expression, resulting in the increase of NO synthesis. In contrast, HIF-2α induces the expression of Arg1, which suppresses the NO production. The balance between HIF-1α and HIF-2α, namely HIF-α switching, regulates macrophage NO production.

cose, but not glutamine, is critically required for macrophage mobilization in hypoxia[51]. Intriguingly, dichloroacetate (DCA), a chemical inhibitor of pyruvate dehydrogenase kinase (PDK) significantly suppressed macrophage migration capacity. These results indicated that glycolysis, but not mitochondrial respiration plays a critical role in maintaining macrophage migration capacity under hypoxic environment.

To further investigate the link between glycolytic metabolism and macrophage migration, we examined the intracellular localization of glycolytic enzymes in macrophages. Pyruvate kinase muscle isozyme (PKM2) belongs to glycolytic enzymes, and is responsible for glycolytic ATP synthesis in the cytosol. Intriguingly, PKM2 co-localizes with F-actin in filopodia and lamellipodia in primary macrophages. These results implied that local production of ATP in the cytosol where it is rapidly consumed during cell migration processes may be beneficial to accommodate the demand of ATP during cell migration processes[52, 53](**Fig. 3**).

We also examined the molecular processes by which hypoxia signaling suppresses glucose oxidation in primary macrophages. We established a novel experimental system in which we could measure the oxygen consumption rate in hypoxic environment. Based on these approaches, we identified a novel mode of glycolytic reprogramming which takes place in primary macrophages, termed as active glycolysis (**Fig. 4**). In active glycolysis, HIF-1α mediated Pdk1 induction actively elicits glycolytic reprogramming even in the presence of mitochondrial electron transport chain activity.

Collectively, these results indicated that cytosolic distribution of intracellular ATP accelerates macrophage motility. Intriguingly, active glycolysis occurs not only in primary macrophages, but also in primary hepatocytes, indicating that this metabolic alteration may be one of the common features in non-malignant cells.

Hypoxia Signaling in Atherosclerosis

Chronic inflammation in the vessel walls underlies the development of atherosclerosis. Various types of the cells including endothelial cells, smooth muscle cells, fibroblasts, monocytes/macrophages and T lymphocytes are involved in atheroma plaque formation. Among them, monocyte/macrophages predominantly promote the progression of atheroma. Foam cells, one of the macrophages in atheroma which is surrounded by the lipid, elicits a fatty streak formation in the vessel walls[54].

The cells of the blood vessel wall depend on the

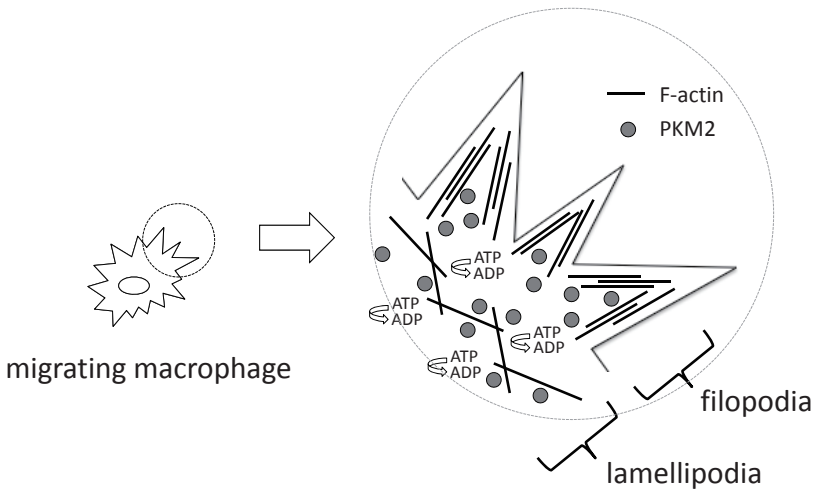

Fig. 3. PKM2 co-localizes with F-actin in macrophages

ATP is consumed at filopodia or lamellipodia during cell migration processes. Pyruvate kinase, muscle (PKM2) co-localizes with F-actin in filopodia or lamellipodia.

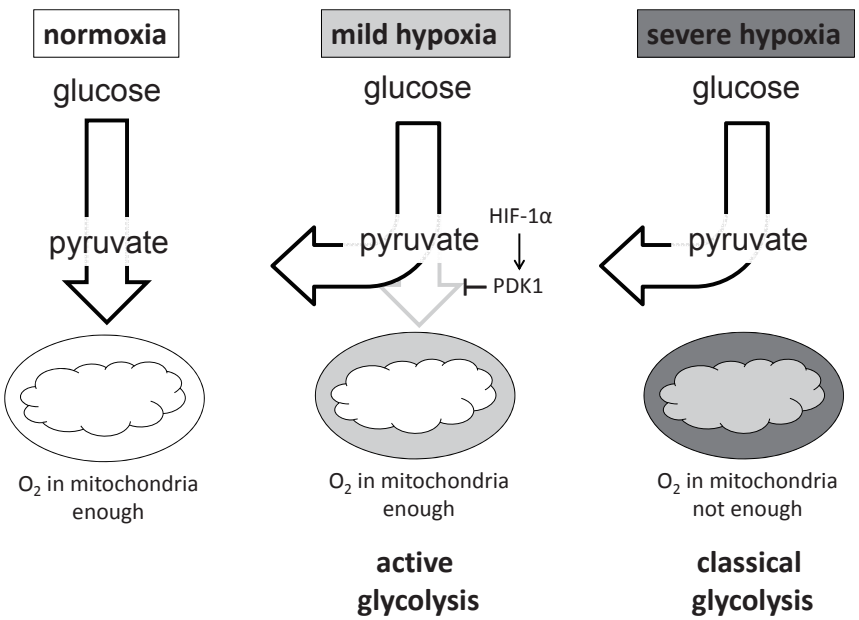

Fig. 4. HIF-1α - PDK1 axis induces active glycolysis in hypoxic macrophage.

In severely hypoxic condition, mitochondrial activity is decreased, resulting in the glycolytic reprogramming (classical glycolysis). In mild hypoxia, HIF-1α - PDK1 axis actively accelerates glycolysis in the presence of sustained mitochondrial activity (active glycolysis).

oxygen supply from the luminal blood or the adventitial vasa vasorum. In developed atherosclerosis, oxygen consumption rate increases in vessel wall, leading to the occurrence of tissue hypoxia at the plaque lesion. Pimonidazole immunohistochemistry, a hypoxia marker, in human atheroma patients revealed that a hypoxic area exists in the macrophage-rich center of the plaque lesion[55]. Intriguingly, HIF-1α is expressed in the macrophages of human atheroma plaques[55-57].

The low-density lipoprotein receptor in deficient mice (Ldlr -/-) is commonly used as a model of atheroma progression. Using this animal model, the roles of macrophage HIF-1α in plaque progression were examined. Bone marrow transplantation of myeloid-specific HIF-1α deficient mice, but not of wild type mice, significantly decreased plaque burden in the

aorta of Ldlr -/- mice. The expression of the genes related to the inflammation or M1 macrophage accumulation was strikingly suppressed in HIF-1α deficient mice[58].

Lectin like oxidized low density lipoprotein (LDL) receptor-1 (Lox-1) is the major receptor for oxidatively modified low density lipoproteins (OxLDLs)[59], and strikingly promotes the progression of atherosclerosis[60]. While Lox-1 is expressed in macrophages, endothelial cells or smooth muscle cells[61, 62], its expression is increased in the hypoxic environment[58]. In agreement with this, macrophage lipid content is significantly increased in hypoxia through a Lox-1 dependent manner. Importantly, HIF-1α in macrophage significantly contributes for the hypoxic induction of Lox-1 gene in hypoxia. These results demonstrate the tissue hypoxia in the plaque lesion is not just a consequence of increased plaque burden, but that in turn, HIF-1α signaling promotes M1 macrophage activation at the center of atheroma plaque.

The roles of HIF-1α signaling, however, in plaque formation seem to be more complicated than expected. CD11c is known as one of the surface markers in antigen-presenting cells (APCs). Conditional ablation of HIF-1α in APCs significantly augment the severity of atheroma formation in Ldlr-/- mice[63]. Accumulation of Th1 at the plaque area was significantly accelerated in APC specific HIF-1α deficient mice.

Collectively, the roles of HIF-1α signaling in each cell during atherogenesis has to be examined in more detail. It still remains unclear as to the molecular processes by which inflammation takes place in the vessel wall. Is it induced through an antigen-dependent or independent process? If there is a specific antigen, what are they? Additional experiments by focusing in the hypoxic signaling will help to elucidate the molecular link between sterile inflammation in atheroma formation.

The Roles of Hypoxia Signaling in Vascular Remodeling

We have shown that the balance between HIF-1α and HIF-2α, namely HIF-α switching, critically regulate the production of NO in primary macrophages. NO also acts as a powerful vasodilator in the circulatory system. NO mediated increase of cyclic guanosine monophosphate (cGMP) in smooth muscle cells regulates vascular tone[64-66]. NO could also elicit vasodilation through a cGMP-independent fashion including S-nitorosylation of target proteins, activation of sarco/endoplasmic reticulum calcium ATPase or production of cyclic inosine monophosphate[67].

Skin is one of the largest organs, and critically regulates systemic vascular resistance through the production of NO. Vasodilation in the skin also works as a radiator and helps to maintain core body temperature. While its vascular tone has to be tightly regulated depending on the external environment, its molecular process still remains unclear. We therefore hypothesized that HIF-α switching regulates vascular tone in the skin, and tested the roles of keratinotye HIF-α signaling in vascular function. We generated keratinocyte-specific HIF-1α and HIF-2α deficient mice (K14-cre; HIF-1α$^{fl/fl}$ or HIF-2α$^{fl/fl}$) and measured systemic blood pressure (BP). While systemic BP is elevated in HIF-1α deficient mice, it is decreased in HIF-2α deficient mice[68]. Cardiac fibrosis elicited by AngiotensinⅡ infusion was also attenuated in HIF-2α deficient mice. These results indicate that HIF-α switching in the skin critically regulates vascular tone in the skin. Consistent with our hypothesis, the core body temperature in HIF-1α deficient mice was elevated when the mice were exposed to the warm environment. Intriguingly, decrease of HIF-1α, but elevation of HIF-2α expression was detected in hypertensive patients, indicating that HIF-α in the skin could contribute in the regulation of systemic BP.

Pulmonary arterial hypertension (PAH) is manifested by an increased BP in pulmonary artery, resulting in the right ventricular heart failure[69-71]. It is also known that a hypoxic environment elicits pulmonary vasoconstriction and arterial remodeling. While hypoxia signaling seems to play pivotal roles in PAH[72, 73], the precise roles of HIF-αs in pulmonary arterial remodeling have been unclear. Hypoxic exposure is commonly used as a murine model of PAH. Recently, the roles of HIF-α switching were examined using hypoxia induced PAH model[74]. Pulmonary endothelial specific HIF-2α deficient mice (L1-cre;HIF-2α$^{fl/fl}$) exhibited tolerance to hypoxia induced PAH compared to control mice or HIF-1α deficient mice. Notably, PA remodeling was significantly attenuated in HIF-2α deficient mice. As a molecular mechanism, HIF-2α mediated induction of arginase-1 critically regulates NO production in pulmonary vasculature.

These results clearly indicated that HIF-2α-Arginase1 axis could become a therapeutic target to improve the NO availability of the pulmonary arteries or systemic circulation. Recently, HIF-2α antagonist was synthesized by using a structure-based design approach, and is currently used to treat patients with renal cell carcinoma[75, 76]. It seems tempting, therefore, to test the therapeutic efficacy of HIF-2α antagonists in PAH. Elucidating the molecular process by which HIF-2α signal is activated in systemic hypertension or PAH will also help to understand the pathophysiology

of vascular remodeling in more detail.

Hypoxia Signaling and Cardiac Remodeling

Hypoxia signaling, as described in the previous section, plays a critical role in the inflammatory process or intracellular metabolism. Importantly, both of them strikingly affect the cardiac function. While heart failure is predominantly a hemodynamic condition, inflammatory signal is strikingly activated in heart failure patients[77, 78]. Serum level of inflammatory cytokines including tumor necrosis factor (TNF)-α or interleukin-6 (IL-6) is significantly elevated in heart failure patients[31]. Importantly, the level of these inflammatory cytokines correlated with the severity of the heart failure[79, 80]. At a histological level, it has also been shown that inflammatory cells including macrophages accumulate to the cardiac tissues of human heart failure subjects[81]. The roles of inflammatory processes in myocardial infarction have been studied using *in vivo* murine model of myocardial infarction[82-84]. Two types of monocytes/macrophages, including Ly-6C^{hi} and Ly-6C^{lo}, sequentially accumulated in response to the myocardial death[85-87]. While Ly-6C^{hi} monocytes/macrophages engulf the injured tissues, Ly-6C^{lo} monocytes/macrophages promoted angiogenesis, and scar formation. These results demonstrate that each population of inflammatory cells exerts a distinct function in cardiac remodeling. These results raised the hypothesis that sterile inflammation underlies the development of heart failure. Two multicenter clinical trials, however, using anti-TNF-α antibody demonstrated that inhibition of TNF-α did not improve the clinical courses of heart failure patients[88, 89]. These results indicate that further study is required to fully elucidate and identify the role of each inflammatory cell in cardiac remodeling.

In physiological condition, the myocardium predominantly utilizes free fatty acids as its energy substrate, and acquires ATP through the oxidative phosphorylation. Molecular oxygen is required to maintain the activity of mitochondrial electron transport chain. Notably, cardiomyocytes change their energy substrates from fatty acids to glucose in response to the mechanical or ischemic stresses[90-92]. We previously reported that this metabolic alteration could become a helpful diagnostic tool in the evaluation of the cardiac function[93].

It still remains unclear whether the metabolic reprograming in cardiomyocytes is an adaptive or maladaptive process in maintaining cardiac function. It has been shown that tissue hypoxia develops during cardiac remodeling processes[94-96]. Moreover, HIF-1α in murine cardiomyocytes plays an important role in modulating its intracellular metabolism by activating PPARgammma[97]. Therefore, elucidation of the hypoxia signaling in cardiomyocytes will help us to understand roles of metabolic alteration in cardiac function.

Conclusion

Tissue hypoxia seems to be one of the common features in cardiovascular disorders including atherosclerosis, vascular remodeling and heart failure. Notably, HIF-α signal has a potential to become a therapeutic target in the managing cardiovascular remodeling. While a number of questions remain unsolved as to the roles of inflammation or metabolic alteration in cardiovascular disorders, further study on the hypoxia signaling will help us to understand its pathological processes in more detail.

Acknowledgement

N.T. was supported by a grant from a Grant-in-Aid for Scientific Research on Innovative Areas "Oxygen Biology: a new criterion for integrated understanding of life" (No. 26111003) of MEXT, Japan. H.A. was supported by Grant-in-Aid for Young Scientists (B) (15K19369, 17K15990).

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N.T. has received grant supports from DAIICHI SANKYO COMPANY, LIMITED, and Bayer Yakuhin, Ltd.. H. S. has received grant supports from The Uehara Memorial Foundation.

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