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Role of Hypoxia Inducible Factors in Obesity Pathogenesis

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Authors' contributions

This work was carried out in collaboration between both authors. Author NY designed the study and outlined the parts. Author HOA wrote the first draft of the manuscript and managed the literature searches. Author NY read through the manuscript and made corrections and also managed the literature searches. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The prevalence of obesity, metabolic syndrome and diabetes has been increasing rapidly worldwide. These are a group of metabolic disorders characterized by a chronic hyperglycaemic condition resulting from defects in insulin secretion, insulin action or both. The control of body weight and blood glucose concentrations depends on the exquisite coordination of the function of several cells, organs and tissues. Underlying mechanisms of obesity and insulin resistance remain uncertain. Adipose tissue is composed of heterogeneous cell types. Immune cells within adipose tissue also likely contribute to systemic metabolic processes. Increased production of local and systemic adipokines and cytokines, polarization of macrophages, T helper subtype changes could contribute to pathologies linking obesity to diabetes, both by decreasing insulin sensitivity, by compromising β-cell function and disturbing adipose tissue metabolism and distribution. Tissue oxygen (O_2) levels, hypoxia inducible factor (s) (HIFs) secretion differences regulate the plasticity of macrophages and the polarization of macrophages controls functionally divergent processes in

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cells. A hypoxic and inflammatory phenotype has been reported in adipose tissue during obesity. Therefore, the present review focuses HIFs-mediated effects of hypoxia in adipocyte inflammation and macrophage polarization associated with obesity pathogenesis.

Keywords: Obesity; pathogenesis; hypoxia inducible factors; inflammation.

1. INTRODUCTION

The incidence of obesity has been dramatically increasing worldwide in both children and adults. The central role of obesity that increase the risk of various diseases including type 2 diabetes, fatty liver disease, atherosclerosis, degenerative disorders and even some cancer types also highlights its importance for the public health [1,2].

During the last decade, the link of obesity with inflammation was clarified by the increased levels of the inflammatory mediators and activation of inflammatory signalling pathways in obesity [3,4]. Hypoxia could be the answer of what induces the chronic inflammation of adipose tissue (AT) in obesity [5]. Hypoxia in obese state may also account the ischemia/reperfusion injury in the AT [6]. The adaptation of cells to hypoxia is mainly regulated by hypoxia-inducible factors (HIFs). Therefore, in this review, we aimed to discuss the HIF signalling thought to be involved in the inflammation, insulin sensitivity, glucose and lipid metabolism in adipose tissue associated with obesity pathogenesis.

2. HYPOXIA IN ADIPOSE TISSUE AND HYPOXIA-INDUCIBLE FACTORS

Chronic, excessive energy intake in obesity, results in AT expansion especially white adipose tissue expansion to increase storage of lipids [7,8]. Despite the expansion, its supporting vasculature does not meet the demand of blood because neither the proportion of the cardiac output or the extent of the blood flow to the tissue is increased [9-12]. The expanded adipocytes also represent larger diameters than the normal diffusion distance for the oxygen [13]. It is also emphasized that a relative adipocyte hypoxia occurs as a result of increased oxygen consumption due to uncoupled mitochondrial respiration during even early in the course of high fat diet-induced obesity [14]. Hypoxia-inducible factors (HIFs) play important role in cellular adaptation to hypoxia. Three members of the family are described as HIF-1, HIF-2 and HIF-3. They have two subunits: O_2-sensitive α-subunit and constitutively expressed β-subunit [15]. Especially, HIF-1α and HIF-2α play important regulator role after heterodimerization with β-subunit by transcription of target genes in response to hypoxia. Although there is limited knowledge about HIF-3α, it is postulated that a negative regulatory role of HIF-3α on HIF-mediated transcription [16]. In normoxia, oxygen-dependent hydroxylation of proline residues of HIF-1α or HIF-2α in by three prolyl hydroxylases (PHD1-3, also known as HIF prolyl 4-hydroxylase (P4H) isoenzymes) makes it ready for polyubiquitination by the von Hippel-Lindau tumour suppressor E3 ligase complex [17-19]. Afterwards, the marked HIFα becomes a target for proteasomal degradation [20]. In addition, also oxygen-dependent hydroxylation of asparagyl residues of HIF-1α or HIF-2α by factor-inhibiting HIF reduces the transcriptional activity of HIF [21]. However, in hypoxia, the diminished level of oxygen stabilizes HIF-1α protein which results in dimerization with HIFβ. Then HIF heterodimers drive the role on gene transcription involved in adaptation to hypoxic stress [22]. Despite HIF-1α and HIF-2α target many common gene expression, HIF-1α is rather associated with glycolytic gene expression [23,24] and HIF-2α-specific target genes are involved in the regulation of function and/or differentiation of stem cell [25], cell cycle progression of renal carcinoma cells [26] and lipid metabolism [27].

It is well known that HIFs are main regulators of metabolism and energy homeostasis. Rahtu-Korpela et al., using HIF P4H isoenzyme 2–deficientmice (Hif-p4h-2–deficient mice), reported that glucose and lipid metabolism were improved and inflammation were decreased in the adipose tissue of the mice than their littermates. The levels of serum total cholesterol and HDL and LDL+VLDL cholesterol and de novo lipogenesis were also found to be decreased in theHif-p4h-2–deficient mice. The improvement in the lipid metabolism seems to be related to increased mRNA levels of the lipolysis markers (i.e. hormone-sensitive lipase and patatin-like phospholipase domain-containing protein 2) in the adipose tissue and decreased mRNA levels of the lipogenic and/or fatty acid synthesis markers (i.e. sterol regulatory element–binding protein 1c and its targets acetyl-CoA carboxylase α and fatty acid synthase) in the liver. The latter

finding could also be explained by the increased mRNA level of insulin receptor substrate-2 [27] which is a targetfor HIF-2α in theliver [28]. Because, insulin receptor substrate protein-2 (IRS-2) is closely linked to lipid metabolism and knockdown of IRS-2 was found to result in theincreasedexpression of lipogenicgenessuch as sterol regulatory element–binding protein 1c and and fatty acid synthase [29]. Ramakrishnan et al. offered further collaborative evidence by demonstrating that extensive liver specific HIF-2α stabilization results in the increased hepatic and serum cholesterol levels [30] (Fig. 1).

HIF-1α, -2α and -3α mRNA expressions have been shown to be increased after prolonged fasting in northern elephant seal pups. The mRNA expression of HIF-1α and -2α was increased 3- to 5-fold in adipose and muscle, whereas that of HIF-3α was increased 5-fold only in adipose of the elephant seal after 7 weeks of fasting. The only HIF-2α protein was detected in the nuclear fractions from adipose and muscle of the elephant seal. Therefore, these findings indicate that HIF-2α plays the main role in the up-regulation of genes involved in the metabolic adaptation during fasting [31].

HIF-3 gene has many variants with different functions [32]. HIF-3α and HIF-2α gene expression was reported to be induced and that of HIF-3α was also regulated by HIF-2α during 3T3-L1 adipose differentiation. Moreover, ectopic expression of HIF-3α in the 3T3-L1 cells was found to be involved in the induction of some adipocytes-related genes and acceleration of adipogenesis [33]. Also role of HIFs could be differing in adipocyte differentiation, HIF-1α levels are decreased during differentiation process of preadipocytes whereas HIF-2 α and HIF-3α expressions are increased in mature adipocytes [33,34].

3. HIFs ARE THE LINK IN BERMUDA TRIANGLE (HYPOXIA-INFLAMMATION-INSULIN RESISTANCE) OF OBESITY

AT has not been any more a simple fat storage organ after Hotamisligil et al. reported a link between in inflammatory cytokine TNF-α and insulin resistance in obese rats [35]. Afterwards, participation of macrophage accumulation in AT of obese mice was shown closely linked with TNF-α and also iNOS and IL-6 expression [36].Later, the realized commonalities of interaction between other effectors of immune system and adipocytes make closer the link of metabolism with inflammation [1]. AT inflammation is now well known as a major contributor to insulin resistance in which characterizes obesity and type 2 diabetes [37]. Under obese conditions, adipose tissue could become oxygen-deficient or hypoxic and then hypoxia induced signalling pathways start to take part in local adipose tissue and systemic crosstalk.

4. THE ROLE OF HIFs IN HYPOXIA INDUCED AT INFLAMMATION

The hypoxia of AT in obesity can induce inflammation by the effects on gene expression. HIF-1α, master regulator of hypoxia, partly drives this effect by induction of target gene expression (i.e. plasminogen activator inhibitor-1 (PAI-1), macrophage Migration-Inhibition Factor (MIF), Inducible Nitric Oxide Synthase (iNOS)) in adipocytes [38] (Fig. 1).

In genetically modified animal models, the role of HIFs in hypoxia-induced inflammation of AT is also questioned. It has been found that hypoxia-induced AT inflammation was decreased with the improvement in glucose tolerance and insulin sensitivity in HIF-1α knockout mice [14,39]. By contrast, mice with genetic deletion of HIF-2α have shown increased inflammation in AT with the impairment in glucose and insulin sensitivity [14]. Interestingly, mice with both genetic deletion of HIF-1α and HIF-2α has shown the phenotypic characteristics similar with HIF-1α knockout mice [14]. It seems to be beneficial effects of HIF-2α could be seen with counter-regulating the deleterious effects of HIF-1α but not alone. AT inflammation by hypoxia is closely linked with insulin resistance and glucose intolerance [40]. But the relationship between HIF-1α and insulin seems to be interdependent. Because insulin can also induce HIF-1α expression in adipocytes especially during adipocyte differentiation [41]. Rahtu-Korpela et al. showed that Hif-p4h-2–deficient mice, whether fed normal chow or a high-fat diet, had less adipose tissue inflammation, increased insulin sensitivity and improved glucose tolerance than their littermates [27]. The latter would be influenced by various factors including increased insulin sensitivity and higher levels of glucose transporters and glycolysis enzymes in their skeletal muscle, adipose tissue and heart through the stabilization of HIF-1α [27,42]. These beneficial effects are also obtained by oral administration of FG-4497 (HIF prolyl hydroxylase enzyme inhibitor) to wildtypemice [27] (Fig. 1).

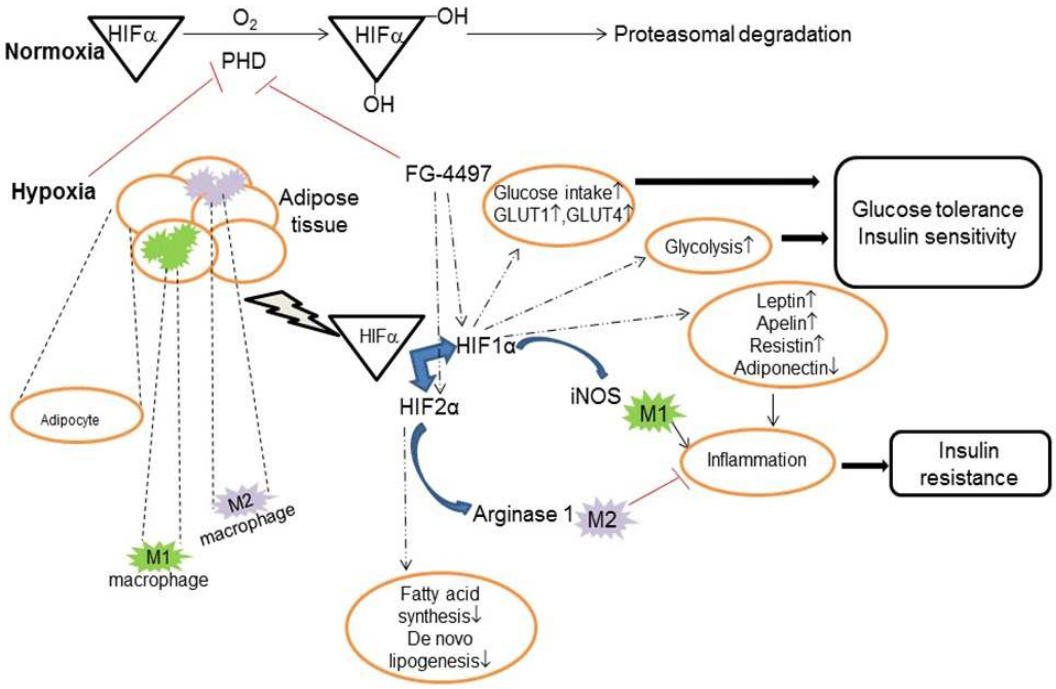

Fig. 1. Schematic diagram of HIF signalling thought to be involved in the inflammation, insulin sensitivity, glucose and lipid metabolism in adipose tissue

Adipokines are proteins that are secreted from adipocytes [43]. Especially, after the discovery of leptin and its increased plasma levels in the obesity has led to focuse on the effects of secretion of such protein signals in AT [5,43]. Later, the plasma levels of some other adipokines have also found increased (i.e. resistin, apelin) or decreased (adiponectin) in a state of inflammation such as in obesity [44-47]. It has been shown that hypoxia stimulates leptin and apelin expression in adipocytes through HIF-1α-dependent manner [44-50]. In HIF-1α knockout mice, the plasma levels of resistin and adiponectin have found to be decreased and increased, respectively [14] (Fig. 1).

5. HIFs EFFECT ON INTRACELLULAR SIGNALLING AND SECRETION OF INSULIN

HIF-1α has some deleterious effects on intracellular signalling pathway of insulin. Akt is the downstream of insulin signalling pathway and nitric oxide (NO) can impair this process by causing nitrosylation of Akt [51]. It has been reported that HIF-1α knockout mice fed with high-fat diet had lower production of NO which resulted in decreased Akt nitrosylation but increased Akt phosphorylation [14]. The other important node in insulin signalling pathway is PI3K [44]. It has been shown that HIF-1α activation by hypoxia, adipogenesis or insulin is required the PI3K/Akt pathway [41].

HIF-1α has not only deleterious effects on insulin sensitivity or insulin signalling pathway but also changes insulin secretion through adiponectin-glucagon-like peptide-1 pathway [39]. Because, glucose tolerance has been found to be improved in adipocyte specific HIF-1α knockout mice due to increased adiponectin serum levels which stimulates glucagon-like peptide-1 secretion [39].

6. HYPOXIA CONTROLS MACROPHAGE DIFFERENTIATION WITH HIFs IN AT

Hypoxia could initiate macrophage infiltration into adipose tissue [8]. AT macrophages have characterizes of proinflammatory (M1 or classically activated) and anti-inflammatory (M2 or alternative activated) phenotypes. Hypoxia also play important role linked with polarization of macrophages to M1 phenotype in AT of obese animals [52,53]. This effect is partly HIF-1α dependent in AT [54]. This phenotypic switch is also important for NO production in macrophages and oppositely orchestrated by HIF-1α and -2α.

Although NO production is increased by HIF-1α via iNOS expression in M1 macrophages, that is decreased by HIF-2α with Arginase 1 expression in M2 macrophages [52,55-57]. Arginase 1 competes for L-arginine with iNOS to produce ornithine and urea instead of NO [58]. The difference in phenotypic profile of macrophages (M1 or M2) also has distinct metabolic pathway choice especially on glucose and lipid metabolism [59]. For example, M1 macrophages choice for rapid energy requirement is an anaerobic pathway like glycolysis such as in hypoxic environment, but that for tissue remodelling and repair is provided by fatty acid oxidation in M2 macrophages [59,60]. The macrophage phenotype which is induced by hypoxia in obesity play important regulatory role on insulin resistance [59]. Although M1 macrophages involved in inflammation and insulin resistance, M2 macrophages promote insulin sensitivity and have preventive role in inflammation of AT [59]. Moreover, AT inflammation and insulin sensitivity has been found closely linked with highly expression of HIF-2α in the M2 macrophages of AT in obese mice [61] (Fig. 1). However, the HIF-2α in AT M2 macrophage-specific effect on whole body insulin sensitivity needs to be clarified [52].

7. CONCLUSION

Obesity is a complex disorder which also predisposes subjects to other diseases including type 2 diabetes. Inflammation is the common key feature in both diseases. Evidence exists that the inflammation could be induced by hypoxia or vice versa. A hypoxic and inflammatory phenotype has been reported in adipose tissue during obesity. The cellular response to hypoxia is principally regulated by HIFs. Therefore, HIFs-mediated dual effects of hypoxia in adipocyte inflammation and macrophage polarization associated with obesity pathogenesis would continue to be important part of the next research topics.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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