ADIPOCYTE
2017, VOL. 6, NO. 2, 147–153
https://doi.org/10.1080/21623945.2017.1288321

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COMMENTARY

The role of glucose-6-phosphate dehydrogenase in adipose tissue inflammation in obesity

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ABSTRACT

Obesity is closely associated with metabolic diseases including type 2 diabetes. One hallmark characteristics of obesity is chronic inflammation that is coordinately controlled by complex signaling networks in adipose tissues. Compelling evidence indicates that reactive oxygen species (ROS) and its related signaling pathways play crucial roles in the progression of chronic inflammation in obesity. The pentose phosphate pathway (PPP) is an anabolic pathway that utilizes the glucoses to generate molecular building blocks and reducing equivalents in the form of NADPH. In particular, NADPH acts as one of the key modulators in the control of ROS through providing an electron for both ROS generation and scavenging. Recently, we have reported that glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme of the PPP, is implicated in adipose tissue inflammation and systemic insulin resistance in obesity. Mechanistically, G6PD potentiates generation of ROS that augments pro-inflammatory responses in adipose tissue macrophages, leading to systemic insulin resistance. Here, we provide an overview of cell type- specific roles of G6PD in the regulation of ROS balance as well as additional details on the significance of G6PD that contributes to pro-oxidant NADPH generation in obesity-related chronic inflammation and insulin resistance.

ARTICLE HISTORY
Received 6 December 2016
Revised 24 January 2017
Accepted 24 January 2017

KEYWORDS
adipocytes; adipose tissue inflammation; glucose-6-phophate dehydrogenase (G6PD); insulin sensitivity; macrophages; NADPH; obesity; reactive oxygen species (ROS)

Obesity is characterized by massively expanded white adipose tissue (WAT) and highly associated with metabolic diseases including type 2 diabetes. In obesity, nutritional stresses disrupt WAT architecture and function, and multiple pathways have been associated with unhealthy WAT expansion.[1] Particularly, compelling evidence indicates that chronic inflammation promotes adipose tissue remodeling and dysfunction including insulin resistance and adipokine dysregulation in obesity.[1,2] The link between obesity and adipose tissue inflammation has been derived after identification of tumor necrosis factor α (TNF α) in obese adipose tissue.[3] The expression of TNF α is elevated in adipose tissues of different rodent models of obesity or diabetes and suppression of TNF α activity by its inhibitor ameliorates obesity-mediated insulin resistance.[3] The reframing of obesity as an inflammatory condition was further supported by studies revealing dramatic accumulation of macrophages and pro-inflammatory responses in obese adipose tissues.[4] Obese adipose tissues secrete several anti- and pro-inflammatory cytokines including interleukin 6, monocyte-chemoattractant protein 1, and interleukin 10.[4,5] Among many cell types in adipose tissue, macrophages have been identified as the primary source of pro-inflammatory cytokines that confer vicious cycle of adipose tissue inflammation through having multiple impacts on other cells.[1,4] In addition to aggravating inflammatory response, macrophage-derived cytokines abrogate insulin signaling in adipocytes through activation of IKKβ/NFκB and JNK pathways.[5-7] There are also clinical reports uncovering insulin sensitizing effects of anti-inflammatory drugs including salicylate in diabetic patients.[8]

Among various intracellular signaling pathways, adipose tissue inflammation is linked to oxidative stress characterized by accumulation of reactive oxygen species (ROS).[9] As visceral fat rapidly expands, adipose tissue generates higher level of ROS in several obese mouse models as compared with their lean littermates.[10] Increased oxidative stress, in turn, potentiates expression and secretion of inflammatory cytokines by activating several transcriptional factors such as NFκB, c-Fos and c-Jun.[11,12] In accordance with animal data, body mass index (BMI) closely correlates with the elevation of

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oxidative stress as well as adipose tissue inflammation in human.[13,14]

ROS is constantly generated by both enzymatic and non-enzymatic reactions in response to external and internal stimuli.[15] Enzyme-mediated ROS production includes those involving NADPH oxidase, xanthine oxidase and uncoupled endothelial nitric oxide synthase (eNOS).[15] The mitochondrial respiratory chain is a non-enzymatic source of ROS.[15] In general, ROS production is buffered through cooperative activity of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase.[15] Balanced activity of ROS generation and scavenging is thus crucial to maintain adequate level of ROS in cells. However, oxidative stress accumulates as a result of excessive production and/or inadequate removal of ROS in various pathological conditions including obesity.[10,16]

As a cofactor and electron donor, NADPH is involved in many key metabolic processes including glycolysis, oxidative respiration, reductive biosynthesis of lipids and redox control (Fig. 1).[9] Metabolically active cells such as adipocytes and hepatocytes utilize NADPH in *de novo* lipogenesis for the α-glycerol phosphate, fatty acids and triglyceride synthesis.[9] The level of NADPH is sustained by different enzymatic systems, e.g. isocitrate dehydrogenase (IDH), which is expressed in both mitochondria and the cytosol, cytosolic malic enzyme (ME) and the pentose phosphate pathway (PPP).[17] Recent studies have shown that dysregulation of NADPH-producing enzymes contributes to obesity and its related complications including lipid abnormalities and dysfunction of metabolic tissues.[18,19] For instance, IDH transgenic mice exhibit obesity, hyperlipidemia, and fatty liver.[18] On the other hand, ME1 deficiency contributes to reduction in obesity accompanied with decreases in fat mass, liver steatosis, and improvement of systemic glucose tolerance.[19]

Additionally, many reports underscore that endogenous NADPH-generating systems serve dual, opposing roles in maintaining ROS balance.[20-22] For instance, antioxidant systems including the glutathione and thioredoxin pathways rely heavily on NADPH for sustaining their activity. NADPH is also the primary substrate for ROS generation by NADPH oxidase (NOX) and inducible nitric oxide synthase (iNOS). NOX and iNOS transfer electrons from NADPH to oxygen and L-argine, generating superoxide and nitric oxide, respectively.[23] Of note, NOX and iNOS have been implicated as pivotal regulators of ROS generation in obese adipose tissue.[24] Several reports demonstrate increments in the expression of NADPH oxidase subunits in WAT of KKAy obese

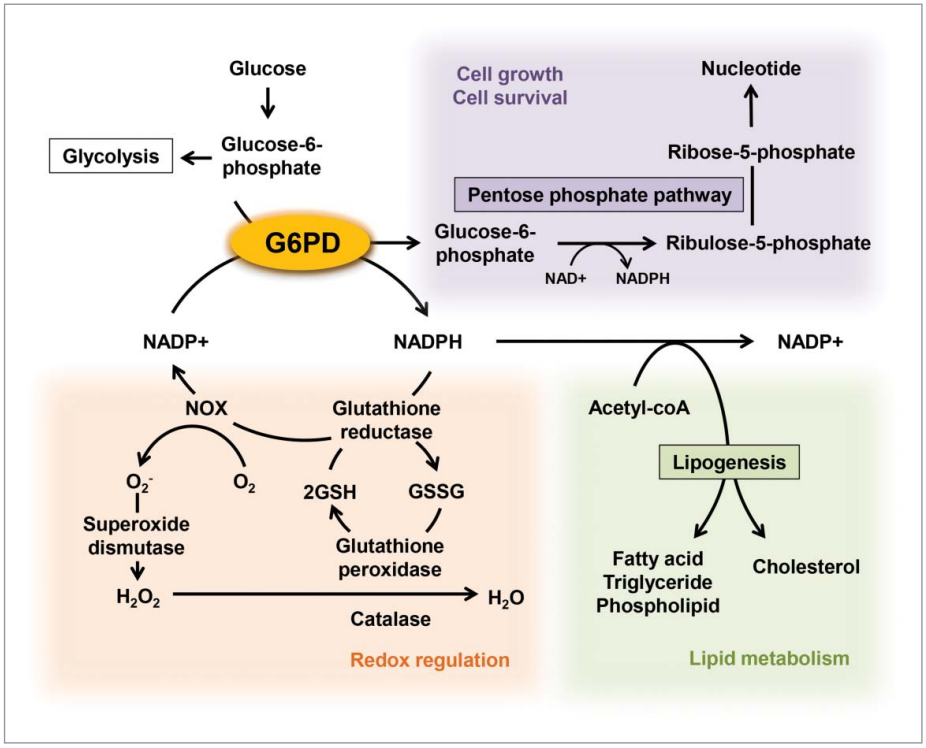

Figure 1. Roles of G6PD in the regulation of cellular metabolisms. G6PD, a rate limiting enzyme of the pentose phosphate pathway, have multiple impacts on a variety of cellular metabolisms through producing NADPH and ribulose-5-phosphate, the latter providing intermediates used for nucleic acid production. NADPH supports the NADPH oxidase (NOX)-mediated ROS generation. On the other hand, glutathione reductase also uses NADPH to reduce oxidized glutathione (GSSG) to reduced glutathione (GSH) for use by glutathione peroxidase that reduces H_2O_2 to H_2O.

mice.[8] iNOS is also upregulated and conspires with NADPH oxidase to activate adipose tissue inflammation and subsequent insulin resistance in obesity.[25] Reciprocally, NADPH oxidase inhibitors mitigate ROS production, pro-inflammatory response and subsequent insulin resistance in obese mice.[26] On the other hand, both expression and activity of enzymes involved in the antioxidant glutathione system tend to be suppressed in obese adipose tissues, which further augments oxidative stress in obesity.[10,27] Both transgene expression of antioxidant genes and antioxidant molecules improve TNF α-induced insulin resistance in adipocytes as well as glucose intolerance in obese subjects.[28]

Among several NADPH-generating systems, the PPP largely accounts for most of cytoplasmic NADPH regeneration compared with other enzymatic systems.[20] The PPP is largely divided into 2 phases: the oxidative generation of NADPH and the nonoxidative interconversion of sugars, the latter providing intermediates used for nucleotide biosynthesis or glycolytic pathway.[29] Glucose-6-phosphate dehydrogenase (G6PD) is a rate-limiting enzyme of the PPP and controls the entry of G6P into the PPP. G6PD catalyzes the conversion of G6P to 6-phosphogluconolactone and the formation of NADPH from $NADP^+$. Therefore, G6PD activity is a key determinant of the cytosolic $NADP^+$/NADPH ratio and consequently contributes to a variety of metabolic pathways that utilize NADPH as a cofactor (Fig. 1).[21]

Multiple lines of evidence suggest that G6PD-derived NADPH has a contradictory impact on ROS level in different cell types (Table 1).[12,30-40] Previous reports highlight that cells with intrinsic susceptibility to ROS predominantly use G6PD-derived NADPH for antioxidant defense in response to oxidative stress. In the case of red blood cells (RBCs), there is constant production of ROS by spontaneous reaction and oxygen oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}). One of the distinct characteristics of RBCs is their large dependence on G6PD-derived NADPH to activate the antioxidant glutathione system as compared with other cells.[31] Since RBCs are not equipped with other NADPH-producing systems, when G6PD becomes dysfunctional, these RBCs become highly susceptible to oxidative stress.[31] Therefore, the most common complications of G6PD deficiency in human is acute hemolytic anemia in response to oxidizing stimuli including microbial infection.[32] Neurons are another cell type that is intrinsically vulnerable to oxidative stress and their antioxidant system is significantly alleviated in response to G6PD deficiency.[33] Given that neurons express antioxidant scavengers and enzymes at a very low concentration/activity, reduction of NADPH level by G6PD deficiency appears to affect ROS scavenging system more than ROS production that is mediated by both NADPH-dependent and independent pathways.[34-36] Moreover, several neurodegenerative diseases are characterized by downregulation of both expression and activity of G6PD in parallel with a decrement of neuronal antioxidant response.[37,38]

Conversely, pro-oxidant pathways in certain types of cell are more sensitive to changes in the level of G6PD-derived NADPH compared with antioxidant pathways. Under stressful conditions, G6PD prominently potentiates ROS generation in several cell types including macrophages, granulocytes, and myocardial cells.[14,41] In the case of myocardial cells, pharmacological inhibition of G6PD

Table 1. Dual roles of G6PD in maintaining ROS balance in a cell type- and tissue-specific manner.

Tissue/Cell type	Pro or Anti oxidative role	Reference
Bovine aortic endothelial cells	Anti	Leopold JA *et al.* (2007) Aldosterone impairs vascular reactivity by decreasing glucose-6-phosphate dehydrogenase activity. *Nat. Med.* 13, 189–197
β cells	Anti	Zhang Z *et al.* (2010) High glucose inhibits glucose-6-phosphate dehydrogenase, leading to increased oxidative stress and β-cell apoptosis. *FASEB J* 24, 1497–1505
Kidney	Anti	Xu Y *et al.* (2010) Glucose-6-phosphate dehydrogenase-deficient mice have increased renal oxidative stress and increased albuminuria. *FASEB J 24*, 609–616
Cardiomyocyte	Anti	Jain *M et al.* (2003) Glucose-6-phosphate dehydrogenase modulates cytosolic redox status and contractile phenotype in adult cardiomyocytes. *Circ. Res.* 93, e9-l 6
Aorta	Pro	Matsui R *et al.* (2005) Glucose-6 phosphate dehydrogenase deficiency decreases the vascular response to angiotensin IL *Circulation* 112, 257–263
Liver	Pro	Gupte RS *et al.* (2009) Synergistic activation of glucose-6-phosphate dehydrogenase and NAD(P)H oxidase by Src kinase elevates superoxide in type 2 diabetic, Zucker fa/fa, rat liver. *Free Radie Biol Med.* 47, 219–228
Heart	Pro	Serpillon S *et al.* (2009) Superoxide production by NAD(P)H oxidase and mitochondria is increased in genetically obese and hyperglycemic rat heart and aorta before the development of cardiac dysfunction. The role of glucose-6-phosphate dehydrogenase-derived NADPH. *Am J Physiol Heart Circ Physiol.* 297, HI 53–62
Adipocyte	Pro	Park J *et al.* (2006) Increase in glucose-6-phosphate dehydrogenase in adipocytes stimulates oxidative stress and inflammatory signals. *Diabetes* 55, 2939–2949
β cell	Pro	Lee JW and Choi AH *et al.* (2011) G6PD upregulation promotes pancreatic β-cell dysfunction. *Endocrinology* 152, 793–803
Macrophage	Pro	Ham *M et al.* (2013) Macrophage glucose-6-phosphate dehydrogenase stimulates proinflammatory responses with oxidative stress. *Mal Cell Biol.* 33, 2425–2435

results in the suppression of ROS generation when exposed to environmental cues causing heart failure.[42,43] Particularly, the pro-oxidant role of G6PD manifests in pro-inflammatory responses of macrophages.[14,44] Mononuclear cells isolated from G6PD-deficient patients secrete fewer pro-inflammatory cytokines than those from normal subjects.[44] Additionally, G6PD is upregulated and augments ROS production and subsequent pro-inflammatory responses in macrophages when challenged with obesity-related stimuli such as free fatty acids and lipopolysaccharide (LPS).[12] In line with *in vitro* data, G6PD expression increases in adipose tissues of both obese mice and obese human individuals, which significantly correlates with increased oxidative stress, adipose tissue inflammation and insulin resistance.[12,42,43] Apparently, macrophages utilize G6PD-derived NADPH to produce ROS that stimulates NADPH oxidase and iNOS expression through activation of NFκB and p38, potentiating vicious cycle of ROS production in obesity.[6,12,42,43] In addition to ROS production, NFκB and p38 promptly induce expression and secretion of pro-inflammatory cytokines in macrophages and mediate adipose tissue inflammation.[14] Suppression of G6PD expression/activity downregulates NADPH oxidase and iNOS, ROS production and mitigates pro-inflammatory response in classically activated macrophages.[12,39,40]

Very recently, the importance of G6PD to adipose tissue dysfunction is substantiated in diet-induced obesity.[45] In agreement with cell culture and *ex vivo* data, G6PD-deficient mutant mice (G6PD^{mut}) display amelioration of adipose tissue inflammation with a concomitant improvement in dysfunction of adipose tissue in obesity. The expression of pro-inflammatory genes decreases whereas the expression of adiponectin, one of the beneficial adipokines, increases in adipose tissue of high fat diet fed G6PD^{mut} mice.[45] Additionally, ROS production and NADPH oxidase expression in adipose tissue are significantly decreased in G6PD^{mut} mice.[45] Together, such changes in adipose tissue result in the improvement of whole body insulin sensitivity and glucose tolerance.[45] One of the distinct phenotypes of G6PD^{mut} mice, which differs from other knockout mice lacking NADPH-producing enzymes, is that there are no significant changes in the lipid synthesis and bodyweight in diet-induced obesity. These phenotypes are of interest as they imply that a decrease in G6PD-derieved NADPH appears to selectively diminish ROS generation without having impacts on lipid synthesis.[45] Molecular mechanisms involved in such selective effect are under investigation. Importantly, adoptive transfer of G6PD^{mut} bone marrow mitigated obesity-induced ROS generation, adipose tissue inflammation, and systemic insulin resistance in

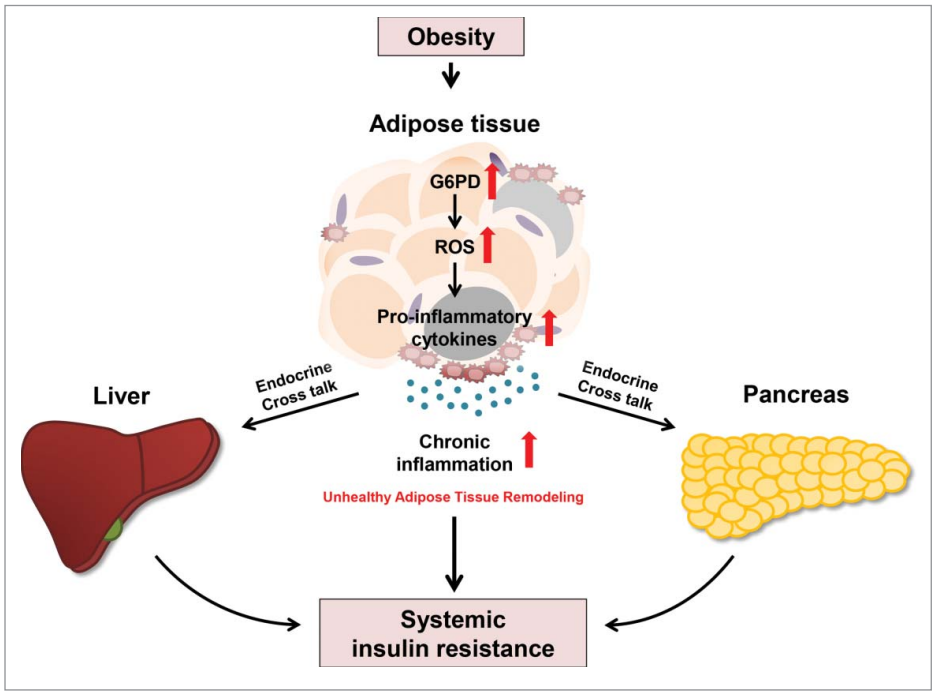

Figure 2. Mechanism by which G6PD drives adipose tissue inflammation and systemic insulin resistance in obesity. Obese adipose tissue manifests in oxidative stress and secretion of pro-inflammatory cytokines in response to metabolic stresses, which is associated with G6PD activation. In obesity, G6PD expression increases and stimulates accumulation of oxidative stress by inducing ROS generation. Increased ROS activates transcriptional factors involved in the expression of pro-inflammatory cytokines. In turn, adipose tissue inflammation elevates and leads to systemic insulin resistance in obesity.

obesity. Previously, it has been demonstrated that G6PD is upregulated in both adipocyte and stromal vascular fraction isolated from obese adipose tissue.[12,39] Moreover, G6PD overexpression *in vitro* stimulates oxidative stress and pro-inflammatory response in adipocytes.[39] Given that G6PD expression is retained in the adipocytes of recipient mice, the results of bone marrow transplantation suggest the relative importance of macrophage G6PD in adipose tissue inflammation and consequent changes in whole body energy homeostasis.[45] In obesity, there is a significant increase in the recruitment of macrophages to adipose tissue, which in turn aggravates adipose tissue inflammation. Thus, a large influx of $G6PD^{mut}$ bone marrow derived macrophages into adipose tissue would overcome the deleterious effects of increased G6PD expression in obese adipocytes.[45]

In conclusion, our recent findings bring to light hematopoietic G6PD as a potential candidate for pharmacological inhibition in the context of obesity (Fig. 2). Although the pathophysiological roles of G6PD manifest in obesity, the underlying molecular mechanisms involved in obesity-induced G6PD expression remain to be elucidated. Previously, we demonstrate that nutrient excess and pro-inflammatory cues increase G6PD expression in both adipocytes and macrophages *in vitro*.[12,39] Furthermore, several studies suggest that hypoxia and enzymes mediating histone modification actively control G6PD expression/activity in various cell types such as neurons and muscle cells.[46-48] Because adipose tissue simultaneously faces those signaling pathways in obesity, further studies are needed to precisely delineate the signaling pathways leading to upregulation of G6PD in obesity. In addition, another open question is what molecular events are responsible for dual, opposing effects of G6PD deficiency on ROS balance in different cell types. A better understanding of such regulation would be important for identifying therapeutic targets for diseases associated with G6PD-induced dysregulation of ROS control.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the National Creative Research Initiative Program of the National Research Foundation (NRF) funded by the Korean government (the Ministry of Science, ICT & Future Planning, 2011–0018312).

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