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REVIEW

Nrf2 in adipocytes

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Abstract White adipocytes play a key role in maintaining whole body energy homeostasis by forming white adipose tissue (WAT). The impairment of WAT formation or WAT dysfunction is clearly associated with severe metabolic disorders. Mature adipocytes are derived from differentiated preadipocytes and are pivotal in energy storage and metabolism. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a member of a family of CNC-bZIP proteins which exert their transcriptional control on genes harboring antioxidant response elements (ARE) in partnership with small musculoaponeurotic fibrosarcoma proteins. The activation of Nrf2-ARE coordinated by specific repressor Kelch-like ECH-associated protein 1 (Keap1) regulates networks of genes controlling diverse homeostatic processes involving adaptive antioxidant response and detoxification among many other adaptive responses. Interestingly, accumulating evidence indicates that Nrf2 may act as a transcription factor in regulating the formation and function of adipose tissues, including adipogenesis, lipid metabolism and insulin sensitivity. In this mini-review, an overview on the distinct roles of Nrf2 in adipocytes is provided. While highlighting the regulatory role of Nrf2 in adipogenesis, recent key findings on Nrf2 in insulin signal transduction and energy metabolism of adipocytes are also summarized.

Keywords Nrf2 · Adipocytes · Adipogenesis · Insulin signaling

Introduction

White adipose tissue (WAT) is composed mostly of adipocytes and is considered to be an active organ that engages in storing and releasing energy, maintains glucose homeostasis, and secretes a variety of adipokines influencing appetite, insulin sensitivity, inflammation, and various other biologically and/or clinically significant pathways (Rosen and Spiegelman 2006; Lee et al. 2019; Chen et al. 2020). With regard to WAT functions in the regulation of metabolic homeostasis of lipid and glucose, excess or ectopic accumulation of WAT is a risk factor for a variety of metabolic disorders, including Type 2 diabetes mellitus (T2DM). Conversely, a severely decreased mass of WAT as observed in lipodystrophy is associated with reduced capacity of WAT to store triglycerides (TGs) and a variety of metabolic disorders (Fig. 1). Therefore, maintaining an appropriate mass and function of WAT is essential for insulin sensitivity and metabolic homeostasis.

Nuclear factor erythroid 2-related factor 2 (Nrf2, also known as NFE2L2), a CNC-basic region/leucine zipper (bZIP) protein, is ubiquitously expressed and serves as a master regulator in both constitutive and inducible expression of antioxidant response element (ARE)-dependent genes, which include many antioxidant and phase II detoxification enzymes (Yamamoto et al. 2018). Thus, Nrf2 has been well investigated as a key factor in many disease

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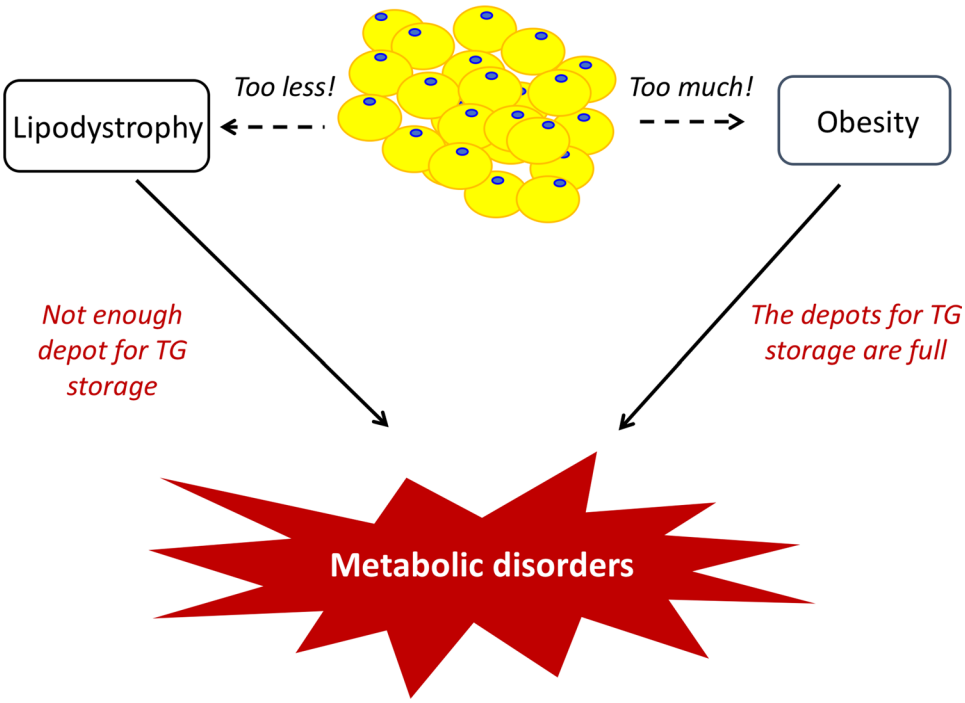

Fig. 1 Functional white adipose tissue is critical for metabolic homeostasis

settings (Li et al. 2020; Wu et al. 2020). Interestingly, accumulating data indicates that Nrf2 may also play critical roles in lipid and glucose metabolism, including adipogenesis and adipocyte function (Pi et al. 2010; Hou et al. 2012; Xue et al. 2013). In this mini-review, we provide an overview on the distinct roles of Nrf2 in adipocyte formation and function. While highlighting the regulatory role of Nrf2 in adipogenesis, recent key findings on Nrf2 in insulin signaling and energy metabolism in adipocytes are also summarized.

Nrf2 and adipogenesis

Signaling cascades in adipogenesis

Adipogenesis is tightly regulated by a multi-step process comprising progenitor commitment and adipogenic differentiation during which fibroblast-like resident preadipocytes are converted to mature, spherical adipocytes with characteristic lipid accumulation (Farmer 2006; Lefterova and Lazar 2009). Firstly, the fibroblast-like multipotent mesenchymal stem cells (MSCs), which are characterized by the expression of platelet-derived growth factor receptor-α (PDGFRα) and/or PDGFRβ, restrict themselves to the adipocyte lineage without any obvious morphological changes, and then form preadipocytes. This cellular commitment is subsequently followed by terminal differentiation, during which selected preadipocytes undergo growth arrest, accumulated lipid droplets and form functional, insulin-responsive mature adipocytes (Farmer 2006; Rosen and MacDougald 2006; Lefterova and Lazar 2009). This complex adipogenic process is regulated by intricate transcription factor networks that coordinate expression of hundreds of proteins responsible for establishing the mature adipocyte phenotype (Farmer 2006; Vishvanath and Gupta 2019). At the center of this network, there are peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα) which together oversee the entire terminal differentiation process (Brown et al. 2018).

PPARγ belongs to a member of the nuclear receptor superfamily and is characterized as the master regulator of adipogenesis, as it is both necessary and sufficient for adipocyte differentiation in vitro (Tontonoz et al. 1994; Al-Ghadban et al. 2020) and in vivo (Sikder et al. 2018) and is also required for maintaining the differentiated state (Tamori et al. 2002). The *Pparg* gene is driven by alternative promoters that give rise to two major protein isoforms, PPARγ1 and PPARγ2 (Zhu et al. 1995). Both isoforms are expressed most abundantly in adipocytes, and PPARγ2 is almost entirely adipocyte specific, while the expression of each isoform is driven by a specific promoter that confers a distinct tissue-specific expression and regulation. Though the relative roles of PPARγ1 and PPARγ2 in adipogenesis remain undetermined (Virtue et al. 2018), studies performed in *Pparg* deletion mouse embryonic fibroblasts (MEFs) demonstrate that ectopic PPARγ1 is capable of inducing adipogenesis as PPARγ2 (Mueller et al. 2002). Furthermore, adipose-selective knockout of *Pparg2* in mice gives rise to insulin-insensitive animals with reduced fat accumulation; however, such mice still contain substantial amounts

of adipose tissues, suggesting that PPARγ1 can compensate for many of the adipogenic functions of PPARγ2. Consistent with murine studies, humans with rare loss-of-function mutations in PPARγ have lipodystrophy and severe insulin resistance (Jeninga et al. 2009). Members of the synthetic thiazolidinedione class of drugs (TZDs) are potent PPARγ ligands that stimulate adipogenesis in vitro and in vivo (Saraf et al. 2012). Although TZDs are generally considered safe, some controversial reports of cardiac side effects and excessive weight gain associated with these drugs have limited the enthusiasm for their clinical application as pro-adipogenic compounds. A series of events including the expression of nuclear retinoic acid X receptor alpha (RXRα), dimerization with PPARγ, then combination with the direct repeat 1 (DR1) site and transactivation of adipocyte-specific genes are key events in adipogenesis, and endogenous PPARγ and RXRα bind to the same repertoire of binding sites in 3T3-L1 cells during early differentiation (Zhang et al. 2018).

The C/EBPs, including C/EBPα, C/EBPβ, and C/EBPδ, belong to the bZIP transcription factor group and are expressed early in adipogenesis (Rosen and MacDougald 2006). C/EBPα and PPARγ form an early positive loop by regulating mutual expression, and then play subsequent roles in a later stage by inducing and maintaining expression of adipocyte-specific genes (Wu et al. 1999). Although forced expression of C/EBPα in fibroblasts can trigger adipogenic differentiation, C/EBPα expression alone is incapable of inducing adipogenesis in the absence of PPARγ (Freytag et al. 1994). In contrast, PPARγ can induce adipogenic differentiation in C/EBPα-null cells, which indicates that PPARγ is sufficient to stimulate adipogenesis (Rosen et al. 2002). C/EBPβ and C/EBPδ are transiently expressed and function at the early stages of differentiation while sensing adipogenic stimuli and initiate the expression of PPARγ and C/EBPα (Yeh et al. 1995). C/EBPβ is thought to trigger the mitotic clonal expansion of preadipocytes and later coordinate the transcription network by turning on C/EBPα and PPARγ (Sikder et al. 2018). The induction of C/EBPβ occurs rapidly upon stimulation of differentiation. Apart from cAMP response element-binding protein (CREB) (Zhang et al. 2004) and Kruppel-like factor 4 (KLF4) (Birsoy et al. 2008), a few transcription factors have been described that bind to the C/EBPβ promoter and positively regulate its transcription during adipogenesis. There are some negative regulators of PPARγ expression, including C/EBP homologous protein (CHOP) and C/EBPγ (Darlington et al. 1998; Pi et al. 2010).

Several additional transcription factors are potential components of the complex network of factors responsible for inducing adipogenic gene expression, such as the helix-loop-helix (HLH) transcription factor sterol regulatory element-binding protein 1c (SREBP1c). Sterol regulatory element-binding proteins (SREBPs) including SREBP-1a, SREBP-1c and SREBP-2 are key transcription factors that regulate fatty acid and cholesterol synthesis (Bertolio et al. 2019). In culture, SREBP1c has been shown to promote adipogenesis by providing lipid ligands that mediate PPARγ activation. Additionally, ectopic expression of a dominant-negative SREBP1c was shown to inhibit preadipocyte differentiation, while overexpression of this HLH protein markedly enhances the adipogenic activity of PPARγ. The forkhead box protein O1 (FOXO1) is a transcription factor that plays an important role in regulation of adipogenesis (Nakae et al. 2003). FOXO1 represses the transcription of the gene encoding PPARγ and is regulated by insulin via Akt-dependent phosphorylation and nuclear exclusion (Nakae et al. 2003).

A considerable number of molecules and pathways identified in murine cell models of adipogenesis have yet been validated in vivo or in human cells. Understanding the intricacies of adipogenesis has clear relevance to human disease, as adipocyte dysfunction is the main risk factor for metabolic disease in obesity. The ability of adipose tissue to influence whole-body metabolism also makes cells within this tissue attractive as pharmacological targets.

Regulation of Nrf2 in adipogenesis

Identifying specific transcription factors that define the preadipocyte population and/or regulate terminal adipogenic differentiation helps providing insights into the signals required to drive multipotent MSCs into adipocytes. Recent studies provided that Nrf2 is an important player in PDGFRα signaling that mediates expression of PDGF-A and adipogenesis (Haider and Larose 2020). Oxidative stress can promote Nrf2 recruitment to the SREBP1 promoter, inducing target gene transcription and subsequent lipogenesis (Sun et al. 2020). As illustrated in Fig. 2, our previous study showed that Nrf2 expression markedly impacts adipogenesis as adipocyte differentiation is inhibited in *Nrf2*-knockout (KO) mice with concurrent downregulation of PPARγ and C/EBPα expression induced by 12-week high-fat diet (HFD) treatment (Pi et al. 2010). Suppression of Nrf2 activity, genetically or chemically, leads to impaired adipogenesis in 3T3-L1 preadipocytes, primary mouse embryonic fibroblasts and/or human subcutaneous preadipocytes (Pi et al. 2010; Chen et al. 2013). Conversely, adipogenic differentiation of 3T3-L1 preadipocytes is enhanced by activation of Nrf2 through knockdown of its negative regulator Kelch-like ECH-associated protein 1 (Keap1) (Pi et al. 2010). Subsequent study showed that C/EBPβ, a critical early regulator for adipogenesis, is regulated by Nrf2 during adipocytes differentiation (Hou et al. 2012). Another study identified binding sites for Nrf2 in the promoter regions of RXRα, which binds to PPARγ to drive the process of adipogenesis (Chorley et al. 2012). Similarly, suppression of Nrf2 attenuates adipogenesis through reducing PPARγ in

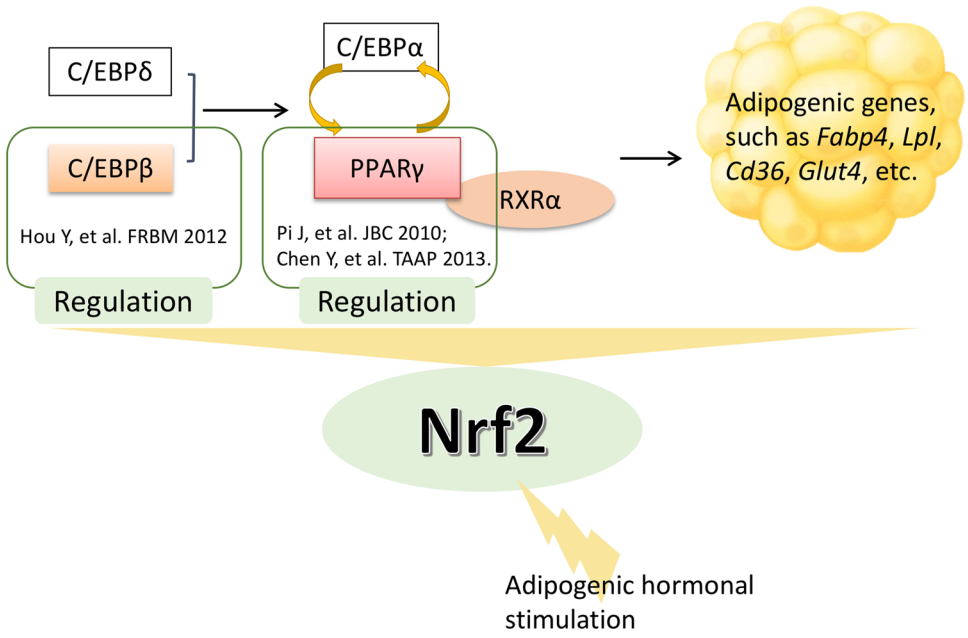

Fig. 2 Regulatory role of Nrf2 in adipogenesis. A series of events including the expression of nuclear RXRα, dimerization with PPARγ, then transactivation of adipocyte-specific genes, are key steps in adipogenesis. C/EBPs are expressed early in adipocytes and play important roles in adipogenesis. Nrf2 has been reported to have a regulatory function in these key stages

3T3-L1 cells (Kim et al. 2018). Likewise, after treatment with sulforaphane (SFN), there was a marked increase in RXRα target gene expression. Knockdown of *Nrf2* results in a delayed expression of RXRα, which, in turn, also results in inhibition of adipogenesis (Shin et al. 2007). In addition, the regulatory roles of Nrf2 in PPARγ expression was further strengthened in non-preadipocyte cell models (Zhan et al. 2012; Li et al. 2020), highlighting that Nrf2 is crucial in other cell differentiation and function via a direct regulation on PPARγ expression.

While extensive studies demonstrated that Nrf2 may function as a positive regulator in adipogenesis, conflicting results also showed that loss of Nrf2 associates with increased differentiation capacity of preadipocytes. Two studies found that Nrf2 inhibits adipogenesis by activating the aromatic receptor (AHR) pathway, which is associated with the impaired differentiation from 3T3-L1 preadipocytes and MEFs to mature adipocytes (Shimba et al. 2001; Shin et al. 2007). In addition, activation of Nrf2 via *Keap1* silencing or chemical activators (SFN or butein) inhibited adipogenesis and reduced expression of differentiation and maturation-related genes such as PPARγ, C/EBPα and fatty acid-binding protein 4 (FABP4), preventing lipid accumulation (Xu et al. 2012; Yang et al. 2017). The inhibitory effects caused by Nrf2 activation is less pronounced when treatment occurs 3 days after initiation of differentiation, suggesting these inhibitory effects produced by Nrf2 are linked to the early stages of adipogenesis. In another study, Nrf2 was shown to have no effect on adipocyte differentiation and function. These authors assessed the mRNA levels of *C/ebpα* and *Fabp4* in WAT of *Nrf2*-KO mice and wild type mice fed with control or HFD for 13 weeks. There was no difference in the expression of these specific adipogenic markers in WAT (Shin et al. 2009), indicating that Nrf2 may involve in the adipogenesis in a time-dependent manner.

Adipocyte differentiation and function can also be affected by cellular redox status, which may be influenced by Nrf2. Recent work demonstrated that adipose tissue mass decreased in insulin resistant NAD(P)H: quinone oxidoreductase 1 (NQO1) knockout (*Nqo1*-KO) mice, revealing a crucial role of NQO1 in adipocyte differentiation and function (Gaikwad et al. 2001). In addition, mice lacking glutamate-cysteine ligase, modifier subunit (*Gclm*) also had a lower body weight and less WAT mass when fed with HFD (Kendig et al. 2011).

The current experimental conclusions do not tend to be unified and the basis for these discrepant results is not known. However, it has been suggested that discrepancies could be due, in part, to the different cell and animal models used in the studies, with major dissimilarities arising when comparing primary cells with immortalized cell lines. In addition, the confounding effects on cell viability and general cytotoxicity cannot be fully excluded from those findings derived from chemical activators and inhibitors. Taken together, Nrf2 clearly exhibits profound effects on adipogenesis through both direct and indirect ways and serves as a very promising target for understanding the mechanisms of adipogenesis and oxidative stress response in adipose tissues.

Nrf2 and adipocyte function

As the main responsive organ of insulin signaling and an important energy storage and transfer tissue, WAT is critical

in maintaining the homeostasis of glucose and lipid metabolism (Kim et al. 2012; Zhu et al. 2019). When adipocyte function is compromised, the free fat acids (FFAs) in the blood cannot be stored safely, which in turn affects on the function of liver and skeletal muscle, aggravating insulin resistance and T2DM (Klöting and Blüher 2014). It has been well documented that enlarged WAT mass and adipocyte size are linked to inadequate vascularization, hypoxia, fibrosis, macrophage infiltration with low-grade inflammation and reduced lipid storage ability and weaken insulin sensitivity (Camporez et al. 2017; Hou et al. 2018; Scherer 2019). In contrast, diminished adipogenesis, such as in lipodystrophy, may also affect WAT function and induce insulin resistance (Vatier et al. 2013; Bindlish et al. 2015). Thus, functional adipocytes in WAT are essential for the homeostatic regulation of glucose and lipid metabolism, whereas Nrf2 has emerged as an important regulator in the complex process.

Nrf2 and insulin signaling

Insulin is an indispensable and vital hormone that coordinates with other molecules to control the blood glucose levels within physiological normal levels to maintain energy homeostasis (Saltiel 2016). As a secreted hormone, insulin's first outstanding feature is the swift response capability based on the cascade phosphorylation signaling pathway rather than transcriptional regulation. To reduce the postprandial glucose level, the secreted insulin recognizes and binds to the insulin receptors (IR) embedded in phospholipid bilayer of cell membranes (Vigneri et al. 2016). Insulin receptor substrate 1 (IRS1) is recruited and phosphorylated by the activated IR, simultaneously generating binding site for SRC-homology 2 (SH2) domains of the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K). Then the p110 subunit of PI3K escapes from the inhibition of p85 and launches the process of conversion, catalyzing the conversion of cytoplasmic phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3), which serves as a vital second messenger. PIP3 binds to pleckstrin homology (PH) domain of its target proteins, and activates many signaling pathways, including most notably protein kinase B (PKB/AKT) pathway. PIP3 can activate the AKT pathway by recruiting the kinases phosphoinositide dependent kinase-1/2 (PDK1/2), which add phosphatidic acid group to AKT at Thr308 and Ser473, respectively (Rodriguez-Escudero et al. 2005). IRS1-PI3K-AKT signaling pathway plays critical roles in apoptosis, autophagy, cell proliferation and metabolism, including glycogen synthesis, gluconeogenesis, lipolysis, fatty acid and cholesterol synthesis (Liu et al. 2015; Chen et al. 2018). Insulin regulates glucose and lipid metabolism mainly in liver, skeletal muscle and WAT (Samuel and Shulman 2016). In WAT, lipolysis process is suppressed by phosphorylated IRS1 (Samuel and Shulman 2016). In contrast, the IRS1-PI3K-AKT signaling pathway facilitates the translocation of glucose transporter type 4 (GLUT4) to the cell membrane to improve glucose uptake (Chen et al. 2018). In the liver, IRS1-PI3K-AKT signaling pathway phosphorylates FOXO1 and then causes its ubiquitination and degradation via proteasome (Matsuzaki et al. 2003). Similar to WAT, insulin increases GLUT2 levels and helps hepatocytes take up more glucose to form glycogen and TGs via a series of transcriptional factors and enzymes, such as SREBP1 and carbohydrate-responsive element-binding protein (ChREBP). A parallel cascade is observed in skeletal muscle, insulin suppresses lipolysis and increases GLUT4 and GLUT1 translocation, thereby promoting glucose uptake and energy storage (Kubota et al. 2017).

Abnormal insulin signaling pathways in adipocytes are often associated with T2DM (Kang et al. 2016). Obesity as a secondary complication is also inevitably involved in the complex metabolic syndrome cycle. Nrf2 is famous for its capability to maintain redox homeostasis and participate in the concurrent insulin resistance and obesity (Fu et al. 2017). The Nrf2 agonist perfluorooctane sulfonate ($C_8HF_{17}O_3S$, PFOS), a chemical widely used in industrial and consumer applications, can enhance insulin-stimulated glucose uptake and increase the expression of *Glut4* and *Irs1* along with the activation of Nrf2 and its downstream antioxidative genes in 3T3-L1 preadipocytes (Xu et al. 2016). Glucoraphanin, a food-sourced Nrf2 inducer, enhances insulin-stimulated Akt phosphorylation on Ser473 in the liver, muscle and WAT of mice under HFD, which coincides with the results of ameliorative glucose tolerance and insulin sensibility (Nagata et al. 2017). In contrast, global *Nrf2*-KO mice showed glucose intolerance and insulin resistance with reduced Akt phosphorylation in skeletal muscle and WAT after insulin treatment (Xu et al. 2015). Expression of *Glut4*, *Irs1* and insulin receptor also displayed a slight decrease in *ob/ob-Nrf2*-KO (Xu et al. 2015) and HFD-fed *Nrf2*-KO mice (Nagata et al. 2017). However, the role of Nrf2 in insulin signal regulation is still controversial. *Nrf2*-KO mice has been shown to exhibit a better glucose utilization, insulin selectivity and increased p-Akt (Ser473) level in liver and skeletal muscle tissues following HFD exposure (Meakin et al. 2014). In hepatocytes, *Nrf2* deficiency resulted in oxidative stress and compromised IGF-IR/IR-PI3K-Akt signal transduction, showing a reduced association of IRS-1 with p85α subunit of PI3K upon insulin administration (Beyer et al. 2008). These results are in line with the finding that Nrf2 mediates hepatitis B virus-induced expression of insulin receptor in hepatocytes (Barthel et al. 2016).

Obese-induced insulin resistance may be partially attributed to impaired adipocyte function and associated inflammation. Both TNF-α and FFAs can activate c-Jun

amino-terminal kinases (JNKs), and inhibit IRS1 phosphorylation at Ser307 and Tyr608 which leads to insulin resistance (Hirosumi et al. 2002; Beyer et al. 2008). In addition, macrophage polarization may affect insulin signaling (Olefsky and Glass 2010). It has been revealed that NRF2-HO-1 can attenuate HFD-induced insulin resistance in mice via effecting anti-oxidation and anti-inflammation (Wang et al. 2017). Several Nrf2 agonists, including resveratrol, glycyrrhizin and omega-3 polyunsaturated fatty acid, reverse exogenous compounds-induced disturbance of glucose homeostasis in WAT via NQO1 in a concentration-dependent way (Baker et al. 2013; Kusunoki et al. 2013; Abo El-Magd et al. 2018). All of these data support a conclusion that exogenous Nrf2 activators may improve the glucose homeostasis and insulin resistance by acting as an anti-inflammatory agent, which reduces pro-inflammatory cytokines that suppress the normal phosphorylation of IRS1-initiated insulin signaling. Another model studied this possibility by using an environmental oxidative stressor, namely low-level inorganic arsenic (iAs) exposure which causes oxidative stress and inflammation. Low-level iAs^{3+} inhibited the insulin-mediated phosphorylation of AKT at the site of Ser473, glucose uptake and GLUT4 activation in differentiated 3T3-L1 adipocytes along with an increase in expression of multiple Nrf2 target genes (Xue et al. 2011), suggesting that a prolonged low-level iAs^{3+} exposure activates the cellular adaptive oxidative stress response involving Nrf2 activation, which impairs insulin-stimulated reactive oxygen species (ROS) signaling, and thus causes insulin resistance in adipocytes.

It has been well documented that mitochondria-derived ROS, such as hydrogen peroxide (H_2O_2), may function as critical messenger molecules to mediate many important physiological responses (Rhee 2006). Previous studies, including our own, indicated that ROS are involved in the regulation of insulin release in β-cells and insulin action in adipocytes and skeletal muscle (Pi et al. 2007; Zhang et al. 2017; Quan et al. 2020). Nevertheless, overwhelming levels of ROS, causing oxidative stress, will lead to β-cell dysfunction/death, chronic inflammation and insulin resistance which induces various signaling pathways including FoxO, mitogen-activated protein kinase (MAPK), JAK/STAT, p53, phospholipase C, PI3K and JNK (Houstis et al. 2006; Zhang et al. 2017). Nrf2 controls a strong mitigating response system to scavenge ROS and protect cells against oxidative damage. To sum up, Nrf2-mediated antioxidant response, on one hand, protects various types of cells from oxidative damage; On the other hand, Nrf2 negatively regulates the levels of intracellular ROS that play an important role in cell signal transduction, insulin signaling in particular. Nevertheless, the interaction between Nrf2 cascade and insulin signaling in adipocytes still needs further investigation.

Nrf2 and lipid metabolism in adipocytes

The TGs in adipocytes may be hydrolyzed into glycerol and FFAs by lipolytic enzymes and released into the blood. FFAs are important secretory products of adipocytes (Wang et al. 2018). Lipolysis is exceptionally sensitive to the action of insulin (Jensen and Nielsen 2007), which constitutes the major antilipolytic pathway in adipocytes. Lipolysis is the sequential hydrolysis of one TG molecule into three FFAs and one glycerol by a class of hydrolytic enzymes commonly known as lipases. Three lipases act in sequence with the concomitant release of one FFA in each step. Adipose TG lipase (ATGL) converts TG to DG and is the rate-limiting enzyme in the lipolytic pathway (Zimmermann et al. 2004). DG is hydrolyzed to MG by hormone-sensitive lipase (HSL) (Haemmerle et al. 2002), and monoglyceride lipase (MGL) cleaves MG into glycerol and FFAs (Heine et al. 2018). In the process, phosphorylation of HSL at Ser563, Ser659 and Ser 660 by protein kinase A (PKA) or via ERK pathway occurs, which leads to HSL translocation to the surface of lipid droplets to activate lipolysis. Lipid droplets in adipose tissue are covered by perilipin-1 (PLIN1), one of the members of the perilipin family. It has been shown that ATGL activity needs to be stimulated by CGI-58 that binds to intracellular lipid droplets through interaction with PLIN1 (Lass et al. 2006). With the increasing number of newly identified enzymes and regulatory proteins, the remarkable complexity of the hormonal and intracellular signaling network regulating the lipolytic pathway has also become clear. It is evident that the balance between lipid mobilization, utilization, and storage is crucial in most tissues.

Activation of Nrf2 can be enhanced by treatment with SFN (Kubo et al. 2017). In vitro data showed that protein expression of both the *Plin1* and *Hsl* genes in adipocytes are significantly reduced after treatment with SFN compared with untreated cells. However, SFN increased phosphorylation of HSL at Ser563 and Ser660 and reduced phosphorylation at Ser565. These findings suggest that SFN-induced adipocyte lipolysis may mediate PLIN1 and HSL expression by stimulating Nrf2 activation (Zhang et al. 2016). Activation of cAMP-PKA-CREB pathway by curcumin, another Nrf2 activator, also plays an important role in lipid homeostasis by increasing lipolysis (Zingg et al. 2017). The Hedansanqi Tiaozhi Tang extract treatment enhanced antioxidant activities and promoted lipolysis in 3T3-L1 adipocytes by activating the Nrf2-HO-1 antioxidant pathway (Qiu et al. 2020). Hyperhomocysteinemia (HHcy) is related to inhibition of adipocyte lipolysis (Li et al. 2018). This research showed that homocysteine (Hcy) exposure is associated with Nrf2 activation, and that deficiency of Nrf2 ameliorated Hcy-induced glycerol release in adipocytes. Conversely, treatment with either epigallocatechin gallate (EGCG) or tert-butylhydroquinone (t-BHQ), two well-known Nrf2

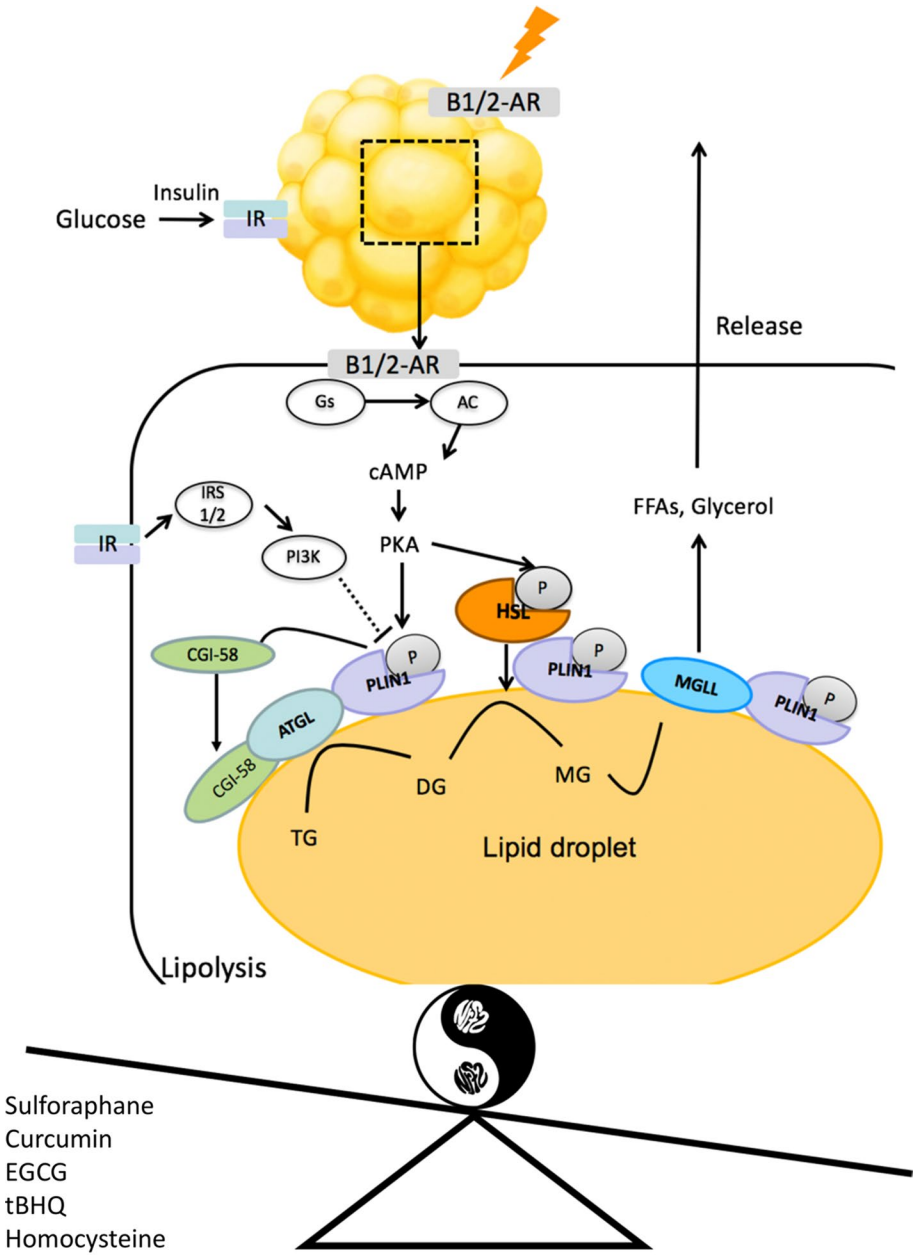

Fig. 3 Paradoxical roles of Nrf2 in lipolysis in adipocytes. Agonists of Nrf2 have shown inconsistent effects on lipolysis. Nrf2 can enhance the lipolysis process by inducing the phosphorylation of lipolytic enzyme. On the other hand, Nrf2 can maintain the shape of lipid droplets, increase the storage of triglycerides and reduce the release of FFAs, suggesting the inhibition of lipolysis process. *AC* adenylyl cyclase, *β1/2-ARs* β-adrenoceptors, *DG* diglyceride, *IR* insulin resistance, *IRS1/2* insulin receptor substrate 1 and 2, *Gs* Gs protein, *MG* monoglyceride, *TG* triglyceride

activators, increased intracellular TG mass and reduced glycerol release in adipocytes (Li et al. 2018). Nrf2 expression and activity can further promote lipid accumulation in adipocytes and exacerbate the development of obesity. In contrast, Nrf2 ablation alleviates oxidative stress-induced lipid accumulation (Sun et al. 2020). Taken together, Nrf2 agonists have shown inconsistent effects on lipolysis. On one hand, Nrf2 can maintain the shape of lipid droplets, increase the storage of TGs and reduce the release of FFAs; on the other hand, Nrf2 can enhance the phosphorylation of lipolytic enzymes (Fig. 3).

Lipogenesis is as significant as lipolysis in adipocyte lipid metabolism. PPARγ acts as a key regulator of adipogenesis to prevent lipotoxicity by not only regulating the development of preadipocytes but also enhancing the lipid storage capacity of mature adipocytes (Medina-Gomez et al. 2007). Previous study showed that FFA re-esterification is mediated by diacylglycerol acyl transferase (DGAT-1), which is an important enzyme participating in the final step of TG synthesis (Chitraju et al. 2017). Interestingly, this re-esterification cycle functions to protect the ER from lipotoxic stress (Chitraju et al. 2017). Others have also found that SFN affects the esterification of FFA. In one particular study, DGAT-1 protein level was significantly reduced in SFN-treated cells compared with control cells (Zhang et al. 2016). Furthermore, there is evidence that enhanced Nrf2

activity resulting from knockdown of *Keap1* decreases FFA transport and results in increased FFA content in WAT (Xu et al. 2013).

Future perspectives

Understanding the regulatory mechanisms of adipogenesis and adipocyte function can greatly aid in defining the molecular pathology of metabolic diseases and the appropriate pharmaceutical intervention. Given the complexity of regulation of adipogenesis and adipocyte functions, an integrated approach is required to investigate the roles of Nrf2 in differentiation and insulin sensitivity in adipose tissues. Understanding how Nrf2 functions in adipocytes is important to comprehending various disease processes, such as diabetes, obesity and related clinical disorders, and could orient pharmacologic interventions aiming at Nrf2 or related systems for prevention and treatment of these common and debilitating human maladies.

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Compliance with ethical standards

Conflict of interest The authors have no conflicting financial interests.

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