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REVIEW

Role of nuclear factor (erythroid-derived 2)-like 2 in metabolic homeostasis and insulin action: A novel opportunity for diabetes treatment?

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Abstract

Redox balance is fundamentally important for physiological homeostasis. Pathological factors that disturb this dedicated balance may result in oxidative stress, leading to the development or aggravation of a variety of diseases, including diabetes mellitus, cardiovascular diseases, metabolic syndrome as well as inflammation, aging and cancer. Thus, the capacity of endogenous free radical clearance can be of patho-physiological importance; in this regard, the major reactive oxygen species defense machinery, the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) system needs to be precisely modulated in response to pathological alterations. While oxidative stress is among the early events that lead to the development of insulin resistance, the activation of Nrf2 scavenging capacity leads to insulin sensitization. Furthermore, Nrf2 is evidently involved in regulating lipid metabolism. Here we summarize recent findings that link the Nrf2 system to metabolic homeostasis and insulin action and present our view that Nrf2 may serve as a novel drug target for diabetes and its complications.

Key words: Nuclear factor (erythroid-derived 2)-like 2; Oxidative stress; Insulin resistance; Metabolism; Diabetic drug

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INTRODUCTION

The association between oxidative stress and insulin resistance has been recognized for more than a decade[1,2]. While the initial interpretation of this phenomenon was that oxidative stress was among the consequences of

impaired insulin action during hyperglycemia[1,2], further studies have revealed the causative role of oxidative stress in insulin resistance[3,4]. More recently, the initiation of oxidative stress in inducing insulin resistance has been more specifically linked to the elevated mitochondrial reactive oxidative species (ROS) production[5]. The progress in the research on the etiological role of oxidative stress in insulin resistance has deepened our knowledge of the patho-physiological alterations in metabolic disorders, including type 2 diabetes mellitus (T2D).

The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) system was originally discovered as one of the important antioxidant machineries[6,7]. In the middle of the 1990s, two teams independently isolated the cDNA that encodes Nrf2[6,8]. The function of Nrf2 in regulating redox balance was identified following the discovery of Nrf2 in up-regulating genes encoding antioxidant enzymes[9]. In addition, another major function of the Nrf2 system in detoxification was revealed[10,11]. The function of this system as a master regulator of redox balance in cellular cytoprotective response is now widely accepted[12].

From practical point of view, Nrf2 has drawn our attention as a promising drug target. Several Nrf2 activators have already been developed for treating diseases, including tumors and inflammatory diseases[13,14]. Interestingly, Nrf2 activators have been shown to modulate insulin action[15]. In addition, certain natural chemicals, including those in the category of Chinese herbal medicine, were shown to both up-regulate Nrf2 action and sensitize insulin action[16]. Further exploration of mechanisms underlying the function of Nrf2 will not only help the proper utilization of traditional medicines in treating metabolic diseases, but also lead to the discovery of novel therapeutic targets for various diseases.

In the past few years, a number of excellent reviews have updated our knowledge about the molecular basis of the Nrf2 system, the crosstalk between Nrf2 and other cell signaling pathways, as well as its capability in repressing inflammation, tumorigenesis and promoting longevity[17-20]. Here we review recent findings which link the Nrf2 system to metabolic homeostasis and insulin action. In addition, we present our view that Nrf2 may serve as a novel drug target for diabetes and its complications.

OXIDATIVE STRESS MAY LEAD TO THE DEVELOPMENT OF INSULIN RESISTANCE

Insulin resistance, i.e., impaired insulin action in its sensitive tissues (muscles, liver and adipose tissue), was recognized as a common feature of obesity and diabetes more than half a century ago[21]. This abnormality is also associated with other prevalent metabolic diseases, including hypertension, dyslipidemia and cardiovascular disorders[22]. The spectrum of insulin resistant syndrome causes a broad health hazard and enormous financial burden, which make the pharmacological combat of insulin resistance an urgent task.

For effective drug intervention of insulin resistance and related diseases, the first important task is to identify a proper drug target. This is based on our understanding the molecular mechanisms underlying insulin insensitivity. Great efforts have been made in the exploration of the cellular aberrant related to insulin resistance. Early observations suggested that the defect in insulin signaling, including insulin receptor substrate-1 (IRS-1), is apparently involved[23]. We have then gradually recognized that the impairment in IRS-1 signaling is not primary but secondary to other alterations[24], including the inflammatory responses (kinase complex IKK-β activation)[25], endoplasmic reticulum (ER) stress[26] and mitochondrial dysfunction[27]. These abnormalities can blunt IRS-1 tyrosine phosphorylation and subsequent insulin signaling transduction[24].

Currently, it is still not known which pathological factor initiates insulin resistance. Several pioneer studies indicated that an apparent impairment of insulin signaling is not prerequisite for the occurrence of insulin resistance in the early stage. A study by Dr. Hoehn *et al*[28] found that treatment of insulin sensitive cells with a variety of insulin resistance inducers, such as tumor necrosis factor-α (TNF-α), oxidative stressor and dexamethasone, did not always impair the insulin signaling transduction, but still produced the impairment in insulin action. Moreover, in mice fed with a high fat diet, leading eventually to initial insulin resistance, there was no insulin signaling alteration involved[28]. This is reinforced by a recent study showing that mitochondrial derived oxidative stress is tightly linked to impaired insulin action, while the traditionally defined insulin signaling transduction appears to be intact[29]. Moreover, in high fat-induced insulin resistance, oxidative stress is evident in adipose tissue at the initial stage of insulin resistance[4,30]. Thus, oxidative stress derived from mitochondrial ROS overproduction after excessive nutrient uptake is likely to be the early aberrance that causes insulin resistance[5]. Furthermore, antioxidants were shown to ameliorate insulin resistance[3]. These findings collectively support the notion that oxidative stress plays an initial role in the development of insulin resistance. This theory also makes sense if considering that insulin resistance is actually an adaptive response to block energy over supply and the mitochondria is a major energy producer responding to energy overwhelming by producing ROS, causing a negative feedback to block insulin action.

Although at this stage we do not fully understand mechanistically how oxidative stress causes insulin resistance, existing scientific evidence has indicated a few potential pathways by which oxidative stress interferes with insulin action. Experimental data indicate that oxidative stress may lead to a direct impairment of insulin signaling molecules *via* modifying their oxidative status[31]. More importantly, oxidative stress can interact with inflammation, ER stress and mitochondrial dysfunction, which are among the causative factors of insulin resistance[25-27].

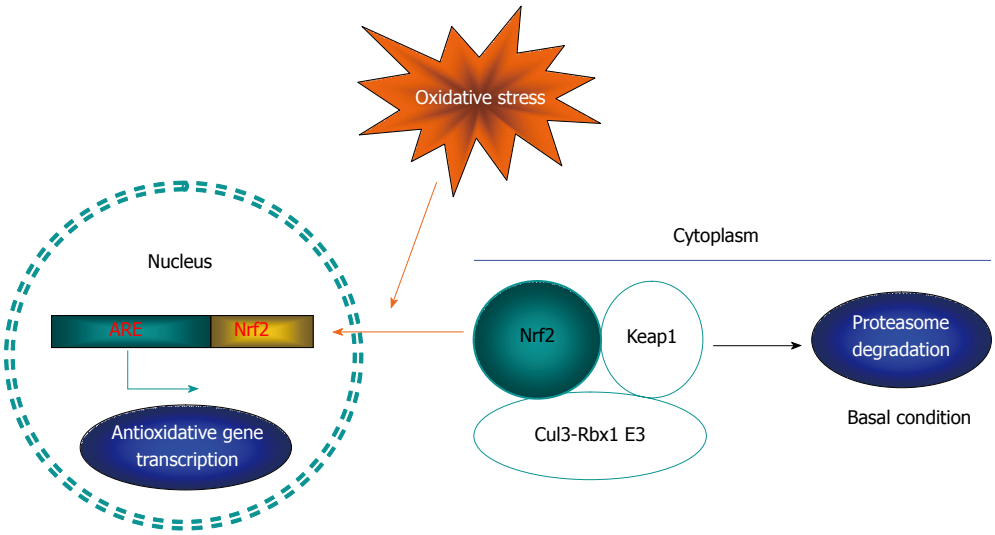

Figure 1 Oxidative stress promotes anti-oxidative gene expression *via* nuclear factor (erythroid-derived 2)-like 2 activation. In a basal state, free Nrf2 level is very low because it forms a complex with Keap1 and the E3 ligase Cul3-Rbx-1, leading to its proteasome degradation. Under the stimulation of oxidative stress, the level of free Nrf2 increases as it is dissociated with Keap1. Free Nrf2 molecules will then enter the nuclei, bind to the cis-element ARE and stimulate the expression of Nrf2 target genes[7]. ARE: Antioxidant response element; Cul3: Cullin 3; E3: Ubiquitin ligase; Keap1: Kelch-like ECH-associated protein 1; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; Rbx-1: RING box protein 1.

While over-nutrition may promote mitochondrial oxidant production and oxidative stress[5], inflammatory signals can be activated by oxidative stress[32]. ER is an initial stress sensing organelle. Responding to oxidative stress, it can also promote the oxidant production by an unfold protein reaction which produces ROS, leading to activation of redox sensitive kinases, such as NF-κB, to initial inflammatory responses[33]. NF-κB-regulated cytokine production in turn negatively affects the function of ER *via* various routes including the increase of TNF-α[34]. One of the fundamental consequences of ER stress response is the inhibition of protein synthesis, which will ultimately affect mitochondrial biogenesis and function[35]. Furthermore, oxidative stress may damage mitochondrial DNA directly and further impair its function[36]. Therefore, oxidative stress is linked to a variety of pathological factors that are important for impairing insulin action.

NRF2 IS AN IMPORTANT ANTIOXIDANT SYSTEM IN EUKORYOTIC ORGANISMS

One of the most important antioxidant machineries is the Nrf2 system, with the transcription factor Nrf2 as the central component[37]. Nrf2 binds to the nucleotide sequence, namely antioxidant response element (ARE), in the promoter region of a battery of genes that encode antioxidant enzymes. The major Nrf2 regulated antioxidant enzymes include heme oxygenase-1, Mn-superoxide dismutase, sequestosome 1, NAD(P)H quinone oxidoreductase 1, glutathione peroxidase, glutathione S-transferase A1 and glutamate-cysteine ligase[37]. Without stimulation, Nrf2 molecules mainly reside in the cytoplasm, anchored with Kelch-like ECH-associated protein 1 (Keap1). The association between Nrf2 and Keap1 may trigger Nrf2 ubiquitination and subsequent proteasome degradation. In response to oxidative stress, certain lysine residues in Keap1 are modified, resulting in the disruption of the complex and the increase of free Nrf2 molecules. Nrf2 free molecules will then be translocated into the nucleus to stimulate gene transcription (Figure 1). Nrf2 nuclear translocation can also be triggered by other signaling kinases. For example, an early study found that ARE-directed transcription was activated by the protein kinase C (PKC) activator, phorbol 12-myristate 13-acetate, while the PKC catalytic subunit was also able to phosphorylate Nrf2 directly *in vitro*, indicating a direct regulation of PKC on Nrf2 translocation and activation[38]. Several other protein kinases, including MARK, PERK and Akt, may also be able to phosphorylate Nrf2 and stimulate its nuclear translocation and action[38-41].

The Nrf2 system is evolutionally conserved and ubiquitously expressed in a variety of cell lineages and systems. This, along with the large spectrum of Nrf2 regulated enzymes, renders it with a great capacity to prevent oxidative stress-induced damage. In addition to its role in regulating redox balance[17,42], recent evidence suggests that the Nrf2 system is involved in certain other important functions, including regulating lipid metabolism and insulin action, which will be detailed in the following sections.

ROLE OF THE NRF2 SYSTEM IN REGULATING INSULIN SIGNALING AND METABOLIC HOMEOSTASIS

The interaction of the Nrf2 system with insulin action is an emerging research theme. In one way, insulin and its effector Akt/PKB were shown to modulate the

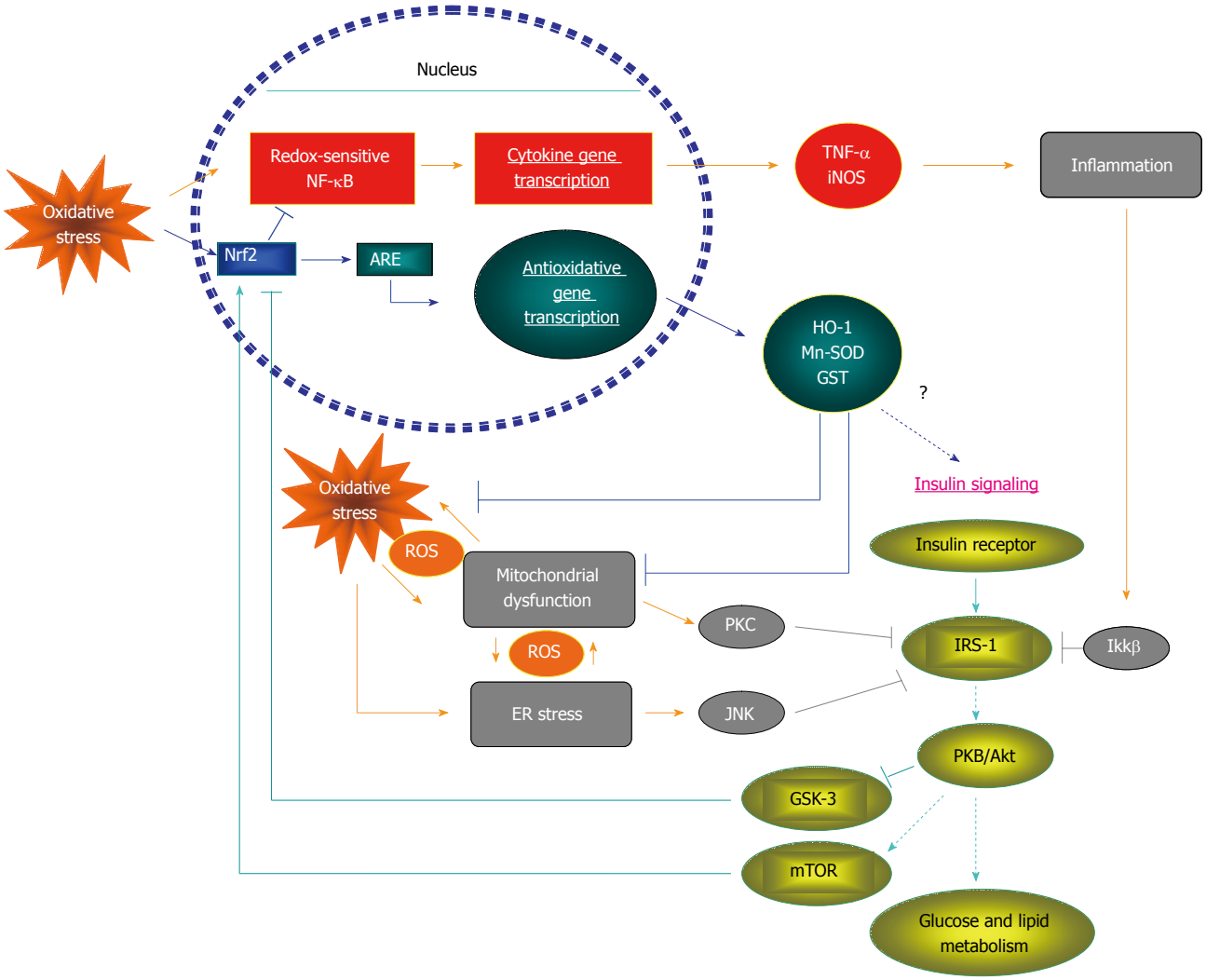

Figure 2 The potential pathways mediate the enhancement of the Nrf2 system on insulin signaling transduction. As a protective machinery, Nrf2 activation promotes the expression of a variety of key anti-oxidative enzymes that scavenge reactive oxidative species, attenuate oxidative stress-induced inflammatory activation, mitochondrial damage and ER stress. Subsequently, Nrf2 enhances insulin signaling by blocking the activation of IKKβ, PKC and JNK, respectively, that promotes the serine phosphorylation of IRS-1 and impairs the tyrosine phosphorylation of IRS-1 as well as subsequent insulin signaling transduction[28]. Furthermore, Nrf2 may directly enhance insulin signaling by an unidentified mechanism[15]. On the other hand, insulin signaling components, such as GSK-3 or mTOR, can promote Nrf2 function by regulating its content and nuclear location[49,50]. The Nrf2 activation, particularly the Nrf2-targeted gene products, heme oxygenase-1 and Mn-SOD, protects from oxidative stress-induced abnormalities and exerts a sensitizing action on insulin signaling[51,52]. ARE: Antioxidant response element; ER: Endoplasmic reticulum; GSK: Glycogen synthesis kinase; GST: Glutathione S-transferase; HO-1: Heme oxygenase-1; iNOS: Inducible nitric oxide synthase; IKK: Inhibitor of κB kinase; IRS: Insulin receptor substrate; JNK: C-Jun N-terminal kinase: mTOR: Mammalian target of rapamycin; Mn-SOD: Mn-superoxide dismutase; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; PKB: Protein kinase B; PKC: Protein kinase C; TNFα: Tumor necrosis factor-α.

function of Nrf2. In *Caenorhabditis elegans* (*C. elegans*), it was shown that Nrf2 (SKN-1, a synonyms in *C. elegans*) can be directly phosphorylated by Akt, leading to the repression of its nuclear translocation[43]. Since oxidative stress is associated with aging and Akt/insulin signaling is a critical signaling that causes aging[44], this repression may be among the mechanisms for insulin signaling in accelerating aging. However, in mammals, a number of studies have actually shown that insulin signaling is required for Nrf2 activation[45,46]. Interestingly, Nrf2 function was found to be defective in aged mice[47] and aging is usually accompanied by insulin resistance. Whether impaired insulin signaling blunts Nrf2 function or the reverse in mammals remains to be examined.

On the other hand, the modulation of the Nrf2 system to insulin signaling in mammals has just been recognized recently, particularly in conditions of insulin resistance. In fact, oxidants are not always detrimental and a certain amount of ROS is important to maintain normal insulin signaling transduction as redox balance is dedicatedly regulated in physiological conditions[48]. However, ROS overproduction will destroy this balance, resulting in oxidative stress and impaired insulin action. To combat oxidative stress, the Nrf2 system may directly or indirectly interact with insulin signaling *via* several potential pathways to sensitize insulin action (Figure 2). It has been demonstrated that in high fat diet (HFD) fed mouse models, Nrf2 activation was shown to repress oxidative

Table 1 Nrf2 system in the regulation of metabolic homeostasis

Effect	Model	Ref.
Preadipocyte differentiation[2]	Carnosic acid and carnosol stimulated Nrf2 activation in 3T3-L1 adipocytes	[54]
Preadipocyte differentiation[1]	Nrf2 deficient 3T3-L1 adipocytes	[56]
Adipocyte differentiation[1]	The Nrf2 activator CDDO-Im-treated mouse embryonic fibroblasts from C57BL/6J Nrf2-/- mice	[62]
Obesity[2]	HFD-induced obesity in C57BL/6J mice fed with the Nrf2 activator oltipraz	[15]
Obesity[2]	HFD-induced obesity in C57BL/6J mice fed with the Nrf2 activator CDDO-Im	[57]
Hepatic lipogenesis[1]	Nrf2 mice deficient mice	[58]
Hepatic steatosis[1]	MCD diet-induced hepatic steatosis in Nrf2 null mice	[59]
Hepatic steatosis[2]	Nrf2-/- mice	[60]
Hepatic gluconeogenesis[1]	STZ-induced diabetes in Nrf2 null mice	[61]
Blood glucose[1], serum lipid[1]	STZ-induced diabetes in Nrf2 null mice	[61]
Blood glucose[2], serum lipid[2]	HFD-induced obesity in C57BL/6J mice fed with the Nrf2 activator oltipraz	[15]
Blood glucose[2]	STZ-induced diabetes in mice treated with oltipraz	[61]
Insulin signaling[1]	HFD-induced obesity in C57BL/6J mice fed with the Nrf2 activator oltipraz	[15]
Insulin signaling[1]	Oltipraz treated- mice with partial hepatectomy	[63]
Insulin signaling[2]	Hepatectomy in Nrf2-/- mice	[53]
Insulin signaling[2]	Nrf2 knockdown in human liver cell line HepG2 cells	[15]
AMPK signaling[1]	Oltipraz treated HepG2 cells	[64]
Pancreatic β-cell damage[2]	Cytokine or STZ-induced RIN β-cell damage with the Nrf2 activator, sulforaphane	[65]
Mitochondria damage[2]	ROS-induced mitochondrial damage in HepG2 cell with oltipraz	[64]

[1]Increase; [2]Decrease. Nrf2: Nuclear factor (erythroid-derived 2)-like 2; CDDO-Im: Oleanolic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9-11)-dien-28-oyl] imidazole; HFD: High fat diet; MCD: Methionine- and choline-deficient; STZ: Streptozotozin; ROS: Reactive oxidative species. AMPK: AMP-dependent kinase.

stress and ameliorate blunted insulin signaling[15]. In addition, Nrf2 activation may enhance insulin signaling *via* inhibiting the inflammation signaling pathway and ER stress *in vivo*[15]. Our group reported recently that a direct depletion of Nrf2 by siRNA in the hepatic HepG2 cell line resulted in impaired insulin-stimulated Akt phosphorylation[15]. Furthermore, in injured liver, Nrf2 was shown to be required to promote liver regeneration in response to Akt activation[53].

In addition to the regulation of redox balance, Nrf2 activation may negatively regulate lipid synthesis and exert an antiobesity function. Several reports have revealed the role of Nrf2 on lipid metabolism in adipocytes. Nrf2 stimulation by carnosic acid and carnosol was shown to inhibit preadipocyte differentiation and adipogenesis[54]. Since adipocyte differentiation is affected by both redox balance and transcription factors[55], we do not know now whether Nrf2 affects adipocyte differentiation through redox modulation or by regulating key transcription factors, such as peroxisome proliferator-activated receptor (PPARγ)[56]. The role of Nrf2 in regulating whole body weight and obesity has been investigated recently by our group and others. Oltipraz and oleanolic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole (CDDO-Im), two known activators of Nrf2, were shown to prevent HFD-induced increase of body weight, adipose mass and hepatic lipid accumulation[15,57]. Importantly, the effects of CDDO-Im were dependent on the Nrf2 system, while no such responses were observed in Nrf2-disrupted mice[57].

In the liver, a recent study using proteomic analysis of Nrf2 deficient transgenic mice suggests that the Nrf2 system is responsible for inhibition of expression of lipid synthetic and metabolic enzymes, such as ATP-citrate lyase[58]. When the methionine- and choline-deficient (MCD) diet was utilized to induce fatty liver, a more profound hepatosteatosis was observed in the Nrf2-null mice, compared with that of the wild type littermates[59]. In contrast, Keap1-null mice showed a delay of onset in hepatosteatosis and the degree of hepatosteatosis was milder than the control wild type littermates[59]. These observations collectively suggest that the Nrf2 system plays a role in repression of hepatic lipid accumulation.

Interestingly, a seemly opposite role of Nrf2 in lipid metabolism and lipogenesis was observed in the analysis of Nrf2-/- mice. These mice show reduced liver weight, hepatic fatty acid content as well as serum lipids[60]. Furthermore, in hepatocytes of the Nrf2-/- mice, the expression level of PPARγ gamma, fatty-acid synthase, stearoyl-CoA desaturase and regulatory-element binding protein that are involved in de novo lipogenesis were found to be reduced[60]. We suggest that the role of the Nrf2 system in lipid homeostasis is certain but complex. The different role of Nrf2 in lipid homeostasis may be related to the status of Nrf2 activation. Permanent inactivation of Nrf2 by genetic modulation versus temporary Nrf2 activation by its chemical activators may give rise different adaptive mechanisms that affect lipogenic gene expression and lipid metabolism.

As Nrf2 affects insulin signaling and lipid metabolism, it is anticipated that Nrf2 would also modulate glucose metabolism. Following STZ treatment, compared with the wild type mice, Nrf2-null mice had a higher blood glucose level, accompanied by enhanced hepatic gluconeogenesis[61]. In the high fat diet-fed C57BL/6J mouse model, the administration of Nrf2 activator oltipraz significantly attenuated glucose intolerance, accompanied by the blockage of the development of obesity and dyslipidemia[15]. Table 1 summarizes the recent findings of the Nrf2 system on metabolic regulation.

NRF2 SYSTEM AS A POTENTIAL DRUG TARGET FOR DIABETES TREATMENT

With the causal link of oxidative stress with insulin re-

sistance[15,66], it is reasonable to expect that Nrf2 activation can be the potential drug target for diabetes treatment[67-71]. Based on existing studies, several aspects of Nrf2 activation can benefit diabetic patients: (1) Nrf2 activation protects pancreatic β-cells from damage[65] and subsequently prevents the onset of diabetes; (2) The sensitizing action of Nrf2 on insulin may bring benefit for diabetic patients with better glucose control; (3) In addition, hyperglycemia-induced endothelial dysfunction, vascular complications and cardiomyocyte damage[72,73] may be prevented by Nrf2 activation by reducing oxidative stress[74-77]; and (4) A protective role of the Nrf2 system in diabetic nephropathy and neuropathy is another potential function for a Nrf2 modulating drug[78-81]. Certainly, to further explore its *in vivo* efficacy, clinical trials are required to prove its usefulness on glucose control and prevention of diabetic complications.

One should note that applying an anti-oxidative stress strategy to treat diabetes was raised a long time ago. However, this approach is questionable because of the experimental observation that exogenous supplement antioxidants, such as vitamin C, do not generate effective and consistent results for the control of glucose level and diabetic complications[81-83]. A potential problem of long-term vitamin C administration with its suppressing effect on the endogenous Nrf2 system[84], therefore, is unable to produce sufficient antioxidant function. The utilization of Nrf2 activator may provide additional advantages compared with external antioxidant intake to treat oxidative stress and prove the effectiveness of this strategy[81].

Natural compounds may provide a rich resource for the pharmacist to explore Nrf2 activators with sufficient safety. Substantial evidence indicates that many natural compounds or nutraceuticals can activate Nrf2[19,85,86]. Notably, resveratrol, curcumin and epigallocatechin-3-gallate are all reported to act as insulin sensitizing agents, reverse hyperglycemia, hyperlipidemia and other symptoms linked to obesity[87-90]. These natural compounds may initially cause a depolarization of mitochondrial membrane potential and ROS production, then activate the Nrf2 system to exert subsequent protective responses[19,91-93]. Furthermore, these plant-derived polyphenols are electrophilic and can modulate the reactive cysteine residues in Keap1 molecules, leading to a dissociation of Nrf2 from the Nrf2-Keap complex and increasing the free Nrf2 level[94,95]. Therefore, released Nrf2 together with the inhibition of Keap1-mediated Nrf2 degradation increases the free Nrf2 level, resulting in its translocation to the nucleus and action (Figure 1). It can be expected that further exploring more potent natural compounds or synthetic derivatives that activate Nrf2 to sensitize insulin action[96] could lead to a new drug generation for diabetes treatment.

CONCLUSION

As the major cellular defense machinery against oxidative stress, the Nrf2 system has drawn extensive attention. However, its functional alteration in metabolic diseases has been realized recently and needs to be explored further. Impaired Nrf2 function is evident in several pathological conditions, such as aging, neurodegeneration diseases and insulin resistance, that are mechanistically linked to oxidative stress, while Nrf2 activation reverses the functional abnormality of these diseases[15,51]. Therefore, the malfunction of the Nrf2 system is anticipated to contribute to the pathological development of these diseases. The characterization of this system in the regulation of glucose and lipid metabolism would evoke more studies to determine if it is a promising drug target. The capability of Nrf2 activation in preventing obesity, protecting pancreatic β cells and enhancing insulin action makes Nrf2 activators a novel category in diabetic therapeutics. Particularly, natural compounds have been proven to be effective in insulin sensitization and preventing diabetic complications in animal and pre-clinical human studies[97]. Further clinical trials are needed to confirm their benefits for diabetics and possible usefulness in clinical treatment. In order to develop Nrf2 activators as therapeutic agents in T2D, we suggest that several tasks need to be carried out for further exploration of the beneficial effects of Nrf2 activation on insulin signaling, as well as glucose and lipid homeostasis: (1) Further investigations are needed to clarify whether and how Nrf2 activation leads to insulin sensitization. Obviously, these investigations may lead to the recognition of novel targets of the Nrf2 system. Nrf2-null mice as well as the *in vitro* Nrf2 knockdown approach are essential tools for this purpose; (2) The Nrf2 system has been shown to be activated by mitochondrial ROS production[98] and when activated can protect mitochondrial function by eliminating ROS[99,100]. Whether this effect is related to its beneficial action in insulin resistance requires further studies; (3) Many natural compounds, such as resveratrol, curcumin and epigallocatechin-3-gallate, have been shown to activate Nrf2, along with improved insulin sensitization. It is essential to determine whether their stimulatory effect on insulin signaling is dependent on Nrf2 activity. Again, the Nrf2 null mice will be the asset for these studies; (4) The AMP-dependent kinase activator metformin, PPARγ agonists and α-folic acid were shown to improve glucose control and also to attenuate oxidative stress[101-104]. Whether these existing drugs exert these effects *via* Nrf2 activation requires further investigations; and (5) Nrf2 can upregulate CD36 expression involved in lipid uptake. However, this effect promotes lipid accumulation in blood vessels and accelerates atherosclerosis[105,106]. While Nrf2 activation can be beneficial to insulin action, these potential side effects must be carefully evaluated.

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