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REVIEW Open Access

Molecular mechanisms and the vital roles of resistin, TLR 4, and NF-κB in treating type 2 diabetic complications

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Abstract

Background: Type 2 diabetes in obese (≥ 25 and ≥ 30 kg/m^2) patients is the foremost cause of cardiovascular complications like stroke, osteoarthritis, cancers (endometrial, breast, ovarian, liver, kidney, colon, and prostate), and vascular complications like diabetic neuropathy, diabetic and retinopathy, and diabetic nephropathy. It is recognized as a global burden disorder with high prevalence in middle-income nations which might lead to a double burden on health care professionals. Hence, this review emphasizes on understanding the complexity and vital signaling tracts involved in diabetic complications for effective treatment.

Main body: Type 2 diabetes in overweight patients induces the creation of specific ROS that further leads to changes in cellular proliferation, hypothalamus, and fringe. The resistin, TLR4, and NF-κB signalings are mainly involved in the progression of central and fringe changes such as insulin resistance and inflammation in diabetic patients. The overexpression of these signals might lead to the rapid progression of diabetic vascular complications induced by the release of proinflammatory cytokines, chemokines, interleukins, and cyclooxygenase-mediated chemicals. Until now, there has been no curative treatment for diabetes. Therefore, to effectively treat complications of type 2 diabetes, the researchers need to concentrate on the molecular mechanisms and important signaling tracts involved.

Conclusion: In this review, we suggested the molecular mechanism of STZ-HFD induced type 2 diabetes and the vital roles of resistin, TLR4, and NF-κB signalings in central, fringe changes, and development diabetic complications for its effective treatment.

Keywords: Type 2 diabetes, STZ-HFD, Resistin, TLR4, and NF-κB signaling

1 Background

Diabetes is a chronic lifestyle syndrome that affects millions of the global population, and it is a significant health issue and obesity plays a vital role in developing diabetes [1]. Diabetes in obese people is a significant cause of stroke, heart attacks, renal failure, impaired vision, and amputation of the lower limb, and type 2 DM is often correlated with obesity and physical inactivity [2].

About 463 million individuals globally have suffered from diabetes and type 2 DM is significantly increasing in middle-income nations with 4.2 million deaths [3]. This is predicted to grow by 2045 to 700 million [3]. In recent years, T2DM accounted for 90–95% of diabetic cases [4].

Therefore, the treatment approaches for T2DM must be designed to reestablish or restore the β cells or its functions, in addition to improving insulin sensitivity [5]. This review indicates the importance of understanding the mechanism (pathophysiology) of disease patterns and specific signaling mechanisms for the discovery of new therapeutic candidates. For this, several animal

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models (spontaneous and induced) are available for the screening of various chemicals and phytopharmaceuticals. The maximum of these induced models cannot be seen as an analogy to clinical situations and the genetic models like ZDF rat and db/db mouse spontaneously develop T2DM similar to humans, but this spontaneous induction of T2DM is not observed in humans [6]. Moreover, these animal models are highly expensive and not easily available for the screening purposes of various novel chemicals. IR and hyperglycemia are attributed to type 2 diabetes in overweight people [7].

Among several type 2 diabetic animal models, the HFD-STZ-induced model is commonly using to discover the novel medicine from various sources (for instance, phytochemicals). In this study, we described the molecular mechanism of streptozotocin and high-fat diet-induced type 2 DM as this model develop similar characteristics to humans [8] and the roles of resistin, TLR4, and NF-κB signaling tracks in diabetic complications for effective treatment of diabetic vascular complications.

2 Main text

2.1 Molecular mechanism of HFD-STZ-induced diabetes

In brief, the streptozotocin (a glucose analog cytotoxic) migrates through the GLUT2 transporter and causes DNA alkylation at the 6th position of guanine moiety of the target β cells by transferring the CH_3 group to DNA leading to DNA fragmentation [9] and protein glycosylation [10]. This results in the initiation of ADP-ribose enzyme to repair the DNA and utilization of energy as ATP which further leads to depletion of cellular ATP and NAD+ stores. This depletion consequences in the establishment of dephosphorylated proteins (substrates for xanthine oxidase) and the invention of ROS (reactive oxygen species) like oxygen and hydrogen peroxides and nitro-methyl-*N*-nitrosourea side-chain proteins, which can liberate hydroxyl and nitric oxide radicals [9].

Further, the excess hydroxyl radical migrates to the cytosol and activates the aconitase, leading to mitochondrial dysfunction and further ATP depletion, which causes the rigorous formation of ROS. All these ROS damage the plasma membrane and necrosis of β cells to induce programmed cell death and decreased insulin availability which causes hyperglycemia [11]. Earlier studies have reported that mitochondrial DNA abnormality, protein alkylation, and glycosylation are also evident for STZ-induced depletion of NAD+, which inhibits insulin biosynthesis and its secretion [12].

This hyperglycemia or diabetes by STZ is dependent on GLUT2 in β cells. The cytotoxicity role of STZ is still not clear. However, several in vitro and in vivo studies have stated that STZ can develop hyperglycemia due to its specific β cell necrosis and apoptosis as a result of oxidative stress and mitochondrial dysfunction [13]. It has also been reported that the cytotoxic effects of streptozotocin are dependent on time and dose to develop oxidative stress, associated alterations of GSH redox metabolism, mitochondrial respiratory, and induction of cytochrome P450 family. This result is important in understanding STZ-induced necrosis and programmed cell death (apoptosis) and the capability of pancreatic cells to breakdown other xenobiotics in stress situations [14]. The proposed molecular mechanism of STZ-HFD-induced diabetes is represented in Fig. 1.

Streptozotocin (STZ) also might cause injury to organs, particularly the kidney, liver, and those expressing GLUT2 transporter [15]. The alkylation in β cell has been described by using ethylating chemicals that are mildly toxic at O^6-ethylguanine than at O^6-methylation [9] and STZ also can affect insulin and glucose homeostasis [16].

HFD-induced obesity increased the levels of TGs (triglycerides) in circulation and in fat cells (adipose) that assist in the progress of IR (insulin resistance) and dysfunction of the adipose cell and tissue [17]. This further increases the insulin level in the blood (hyperinsulinemia) where the body tissues become insensitive to insulin and inflammation [18]. The pathophysiology linking to inflammation in metabolic illness and complications has stimulated interest in targeting inflammatory pathways to prevent or manage diabetic complications [19]. The mechanism of β cell damage via free radical generation is not only specific for STZ. This can be applicable for other diabetogenic chemicals (for instance, alloxan monohydrate) that induce the pancreatic β cell oxidation via free radical generation in obese individuals. Among the various methods of induction, the combination of HFD and STZ will develop similar characteristics to humans [8]. Hence, we selected this model to provide the molecular mechanism type 2 diabetes pathogenesis and to identify the various signaling pathways for effective management of diabetic complications.

2.2 Diabetic complications via NF-κB

Diabetic complications are linked with prolonged persistence of insulin resistance and hyperglycemia [20]. The elevated glucose level in the blood (hyperglycemia) induces the creation of ROS, AGEs (advanced glycation end-products) protein kinase-C (PKC), and AT-II due to increased polyol flux, hexamine flux, PKC activation, and accumulation of AGEs [21–23]. These intermediate biomolecules are the key factors for the activation of the NF-κB signaling pathway [21, 23]. The schematic representation of diabetic complications is shown in Fig. 2.

2.3 Diabetic neuropathy

Diabetic peripheral neuropathy (DPN) and diabetic autonomic neuropathy (DAN) are the intensive and most

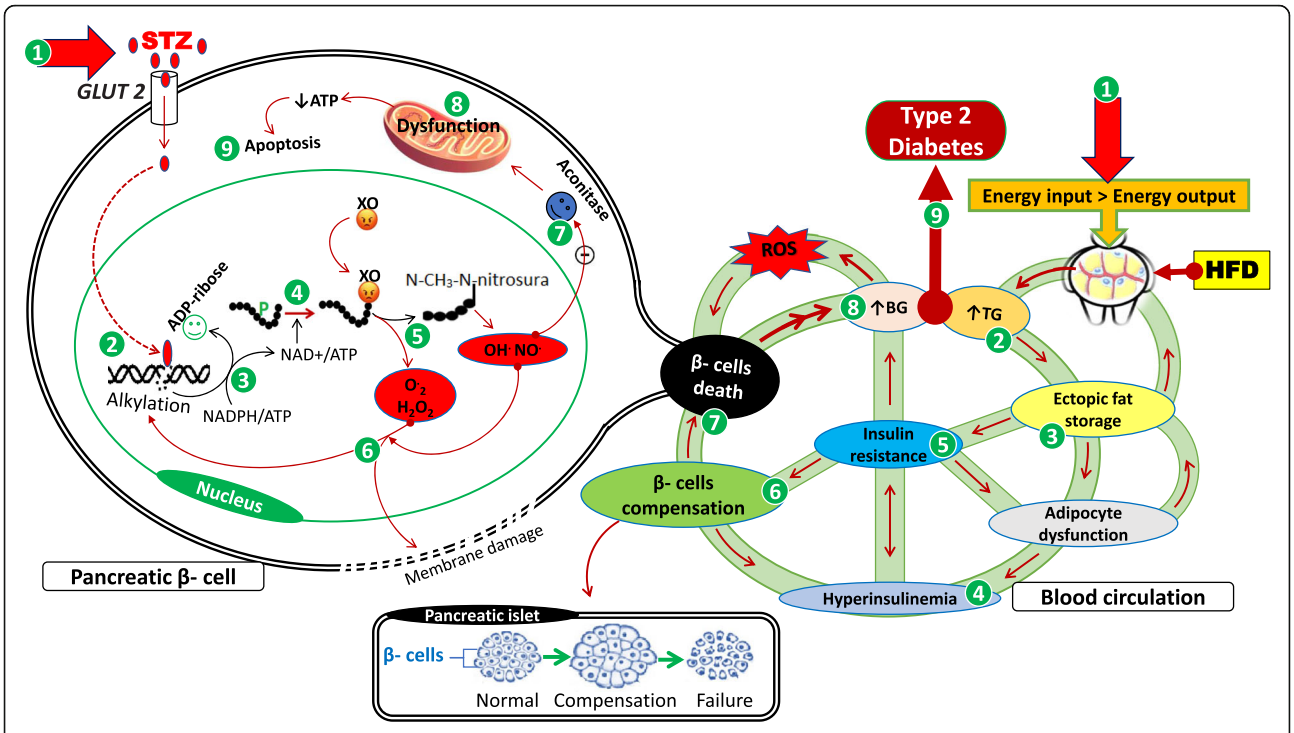

Fig. 1 Molecular mechanism of STZ-HFD induced type 2 diabetes. → : Initiation/release/damage; → : Repair/remodeling; ⊕: Stimulation; ⊖: Inhibition. HFD high-fat diet, TG triglycerides, BG blood glucose, ROS reactive oxygen species, GLUT2 glucose transporter 2, ADP adenosine diphosphate, NADPH nicotinamide adenine dinucleotide phosphate, APT adenosine triphosphate, NAD nicotinamide adenine dinucleotide, XO xanthine oxidase, and free radicals ($O^{\cdot}_2$, H_2O_2, $OH^{\cdot}$, $NO^{\cdot}$)

severe type of vascular diabetic complication and often the principal cause of a significant rise in morbidity and mortality [24] which comprises the loss of sensation; peripheral, somatic, autonomic, and motor dysfunction; axonal thickening; loss of nerve fibers; demyelination; narrowing of the neural capillary system, and elevated MAPK that leads to nerve injury [25]; the schematic representation of pathogenesis (Fig. 2). The hyperglycemic condition triggers the AGE/RAGE formation in neurons [23], and increased HbAc1 and collagen in peripheral nerves are also an additional risk factor for diabetic nephropathy [26].

The NF-κB gets activated by AGE/RAGE and causes the release of TNFα [21, 27]. The augmented concentration of sorbitol can increase due to increased polyol flux by aldose reductase (AR) and the generation of ROS in neural cells [28]. The sorbitol and ROS affect nerve conduction by inhibiting sodium-potassium ATPase which delays in conduction velocity in the nerves and weakness [29]. The overstimulation of NF-κB also leads to the infiltration of leucocytes, reduced neural growth factors (NGFs), increased TNFα, and IL-6 in nerve cells [30]. Simultaneously, the cyclooxygenase-2 (COX-2) is also gets activated as a result of the arachidonic acid pathway expression [31]. Elevated ICAM and NF-κB are noticed in sciatic-tibial nerves of diabetic rats that cause the narrowing of blood vessels and ischemia with inflammation [27]. The peroxisome proliferator-activated macromolecular receptors are declined in the nerves as a result of elevated levels of cytokines which increase neural death [32].

2.4 Diabetic nephropathy

Diabetic nephropathy is the principal reason for cardiovascular and chronic kidney diseases characterized by reduced GFR, microalbumin, and increased albumin-creatinine ratio [33]; the schematic representation of pathogenesis (Fig. 2). Renal inflammation is a significant factor in the evolution of diabetic nephropathy. Pro-inflammatory cytokine molecules are accountable for the infiltration of various macrophages, monocytes, and T cells [34, 35].

Apart from this, the leucocytes can upregulate the NF-κB in endothelial and mesangial cells [35, 36], thus stimulating MCP-1, leading to macrophage infiltration [37, 38], and increased microalbumin and renal injury [39, 40]. The activated NF-κB also activates MAPK and enhances the response of TGF-β-activated kinase (TAK1) released from the MAPK family (MAPK3K7). The TAK1 in turn stimulates the TGF-β, which develops the fibrosis and extracellular matrix accumulation [41]. MAPK also contributes to the overexpression of various

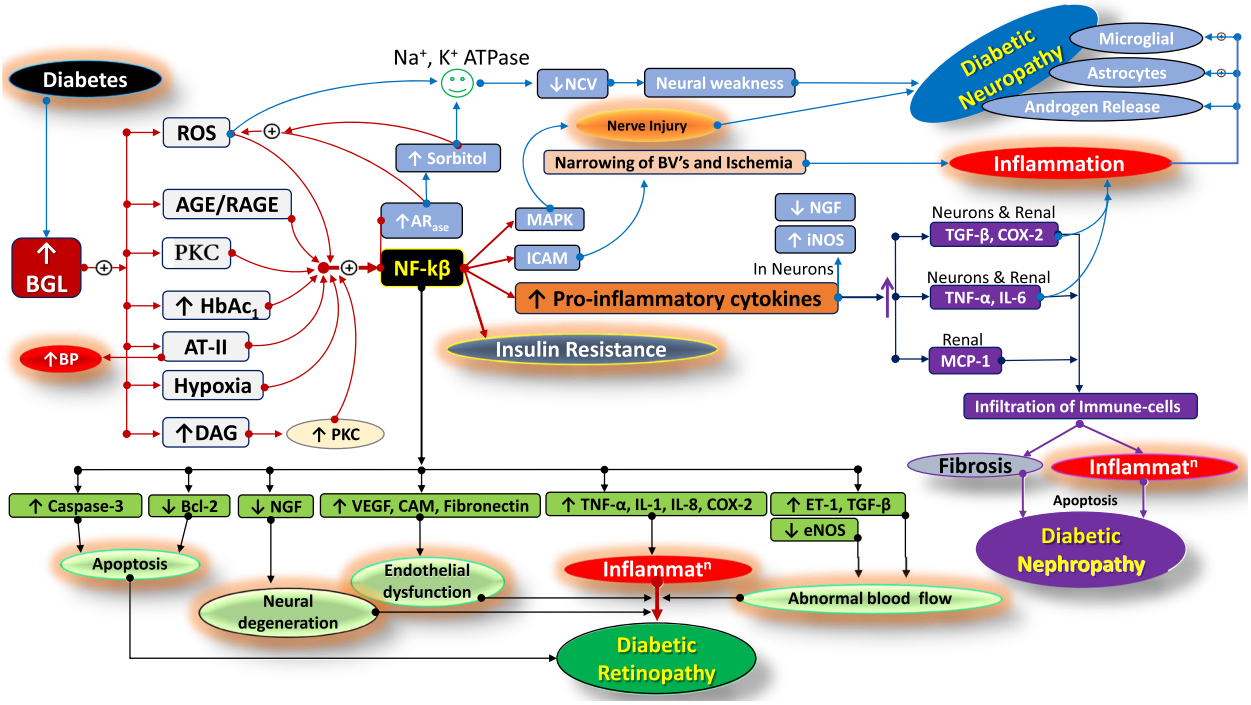

Fig. 2 Role of NF-κB signaling pathway in diabetic complications. →: Stimulation/release; →: Pathway of diabetic neuropathy; →: Pathway of diabetic nephropathy; →: Pathway of diabetic retinopathy; ⊕: Stimulation; ⊖: Inhibition. BGL blood glucose level, BP blood pressure, ROS reactive oxygen species, AGE/RAGE advanced glycation end products/receptor for advanced glycation endproducts, PKC protein kinase C, $HbAc_1$ glycated hemoglobin, AT-II angiotensin II, DAG diacylglycerol, NF-kB nuclear factor kappa-light-chain-enhancer of activated B cells, AR_{ase} aldose reductase, MAPK mitogen-activated protein kinase, ICAM intercellular adhesion molecule, NCV nerve conduction velocity, NGF nerve growth factor, iNOS inducible nitric oxide synthase, TGF-β tumor necrosis factor-beta, COX-2 cyclooxygenase-2, TNF-α tumor necrosis factor-alpha, IL-6 interleukin-6, MCP-1 monocyte chemoattractant protein-1, Bcl-2 B cell lymphoma 2, VEGF vascular endothelial growth factor, CAM cellular adhesion molecule, IL-8 interleukin-8, ET-1 endothelin 1, eNOS endothelial NOS

genes in releasing the cytokine molecules and intracellular adhesion molecule (ICAM), JNK, and leucocyte infiltration via NF-κB activation [27]. Angiotensin-II (AT-II) also upsurges as a result of AGEs and oxidized lipids in DN patients. This triggers the NF-κB via a canonical pathway, and further inflammation can develop in the kidney and cause injury [27, 42].

2.5 Diabetic retinopathy

Diabetic retinopathy (DR) is the greatest and specific microvascular complication and leads to blindness in diabetic patients [43]. It is indicated by pericytes loss, condensing of the capillary basement membrane, cataract, capillary cellularity, microaneurysm, and blood-retinal barrier [44]. Based on its severity, the DR is classified as proliferative-diabetic-retinopathy, non-proliferative-diabetic-retinopathy, and diabetic-macular-edema [45]. As per the current information, 1/3 of the estimated 285 million diabetic patients have signs of DR [46]. The development of retinopathy in the USA was estimated at 28.5% and 4.4%, respectively [44]. The schematic representation of pathogenesis is shown in Fig. 2.

The mechanism of nephropathy in diabetic patients is not well understood and described, even though many proposed pathogenic have been described, viz. increased AGEs, increased ROS, PKC, aldose reductase, and cytokines [44, 47]. The inflammation plays a major role in DR pathogenesis, and the increased levels of ROS and AGEs activate apoptotic cell death [48].

Stimulated NF-κB will increase the specific proinflammatory mediators and cytokines like tumor necrosis factors (TNFs) and IL capsase-3 that cause inflammation and cell death [49]. Further, the inflamed cells release the nitric oxide (NO) leading to the stimulation of NO synthase, which can cause the narrowing of vessels, ischemia, and flow abnormalities [50]. The release of ICAM-1, CD18, and fibronectin enhances the infiltration of leucocytes, fibrosis of retinal space, and breakdown of the retinal-blood barrier [51].

Elevated PKC and imbalance in pro-NGF and NGF further develop the neural damage or dysfunction in the retina and enhance the polyol flux and MAPK, TNFα, and COX-2, leading to enhanced inflammation [27]. Matrix metalloproteins, especially MMP-9, also play a crucial role in angiogenesis and cell death (apoptosis) in DR. These protein levels are elevated in vitreous and

retina in both animal models and diabetic patients [52]. Elevated ILs and MMP-9 also cause DNA alkylation and progression of DR [53].

2.6 HFD/obesity-induced hypothalamic, fringe changes

Obesity, a nutritional disorder, is the foremost health concern in developing countries which is the major concern in the advancement of T2D and atherosclerosis cardiovascular complications like stroke [54]. Cholesterols or triglycerides in overweight patients develop the insulin resistance and the epidemiological findings stating that insulin resistance has been related to abridged tissue sensitivity to insulin and raised pro-inflammatory mediators [55]. The schematic representation of these changes is shown in Figs. 3 and 4. These mediators are also amplified in the brain of rodents in HFD-induced metabolic inflammation, which plays a significant role in insulin resistance [56]. Primarily, this type of inflammation in the adipose tissue might lead to the release of pro-inflammatory biomolecules [57]. These mediators can able to alter sensitivity to insulin in the skeletal muscle, adipose tissue, and in the liver [57]. The HFD activates the local immune components in the mediobasal hypothalamus to release proinflammatory mediators which cause the neural injury [58].

The mechanism of pathogenesis of obesity-induced inflammation in the hypothalamus, and fringe insulin resistance is still not clear, but in this context, of a few potential pro-inflammatory pathways has been proposed. ROS plays a vital role in obesity and insulin resistance (IR) by inducing inflammation, oxidative stress, mitochondrial dysfunction, and ER stress [59]. JNK encourages the serine phosphorylation of IRS-1 and inhibits insulin-dependent tyrosine phosphorylation and downstream signaling [59, 60]. The NF-κB signaling activates and upregulates SOCS3, and the PTP1B proteins could be linked to inflammation and IR in the central hypothalamus [61] and the deficiency of JNK in the brain defends against HFD-induced insulin resistance [62]. The IKK-β/NF-κB pathways also have a critical part in the

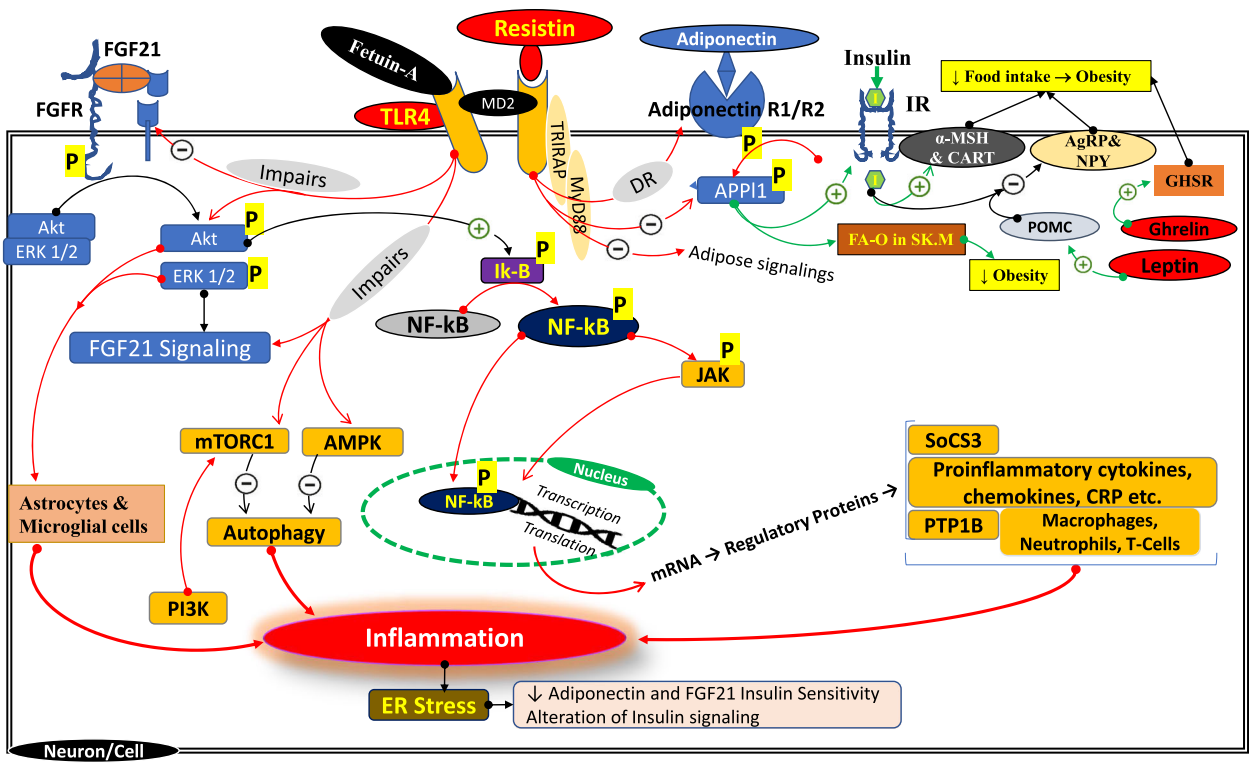

Fig. 3 Role of resistin, TLR4, and NF-κB signalings in the development of inflammation. →: Stimulation/release →: Restore/repair; ⊕: Stimulation; ⊖: Inhibition. FGF21 fibroblast growth factor 21, FGFR fibroblast growth factor receptor gene, Akt protein kinase B, ERK extracellular signal-regulated kinases, MD2 myeloid differentiation factor 2, TLR4 Toll-like receptor 4, TRIRAP Toll/interleukin-1 receptor domain-containing adapter protein, NF-kB nuclear factor kappa-light-chain-enhancer of activated B cells, Ik-B IκB kinase, mTORC1 Mammalian target of rapamycin complex 1, AMPK AMP-activated protein kinase, PI3K phosphatidylinositol-3-kinase, JAK c-Jun N-terminal kinases, MyD88 myeloid differentiation primary response 88, DR diabetic retinopathy, APPI1 adaptor protein, phosphotyrosine interacting, IR insulin resistance, α-MSH & CART α-melanocyte-stimulating hormone & cocaine and amphetamine-regulated transcript, AgRP& NPY Agouti-related protein & neuropeptide Y, GHSR growth hormone secretagogue receptor, POMC proopiomelanocortin, FA-O in SK.M skeletal muscle lipid oxidation, SoCS3 suppressor of cytokine signaling 3, PTP1B protein tyrosine phosphatase 1B, ER endoplasmic reticulum

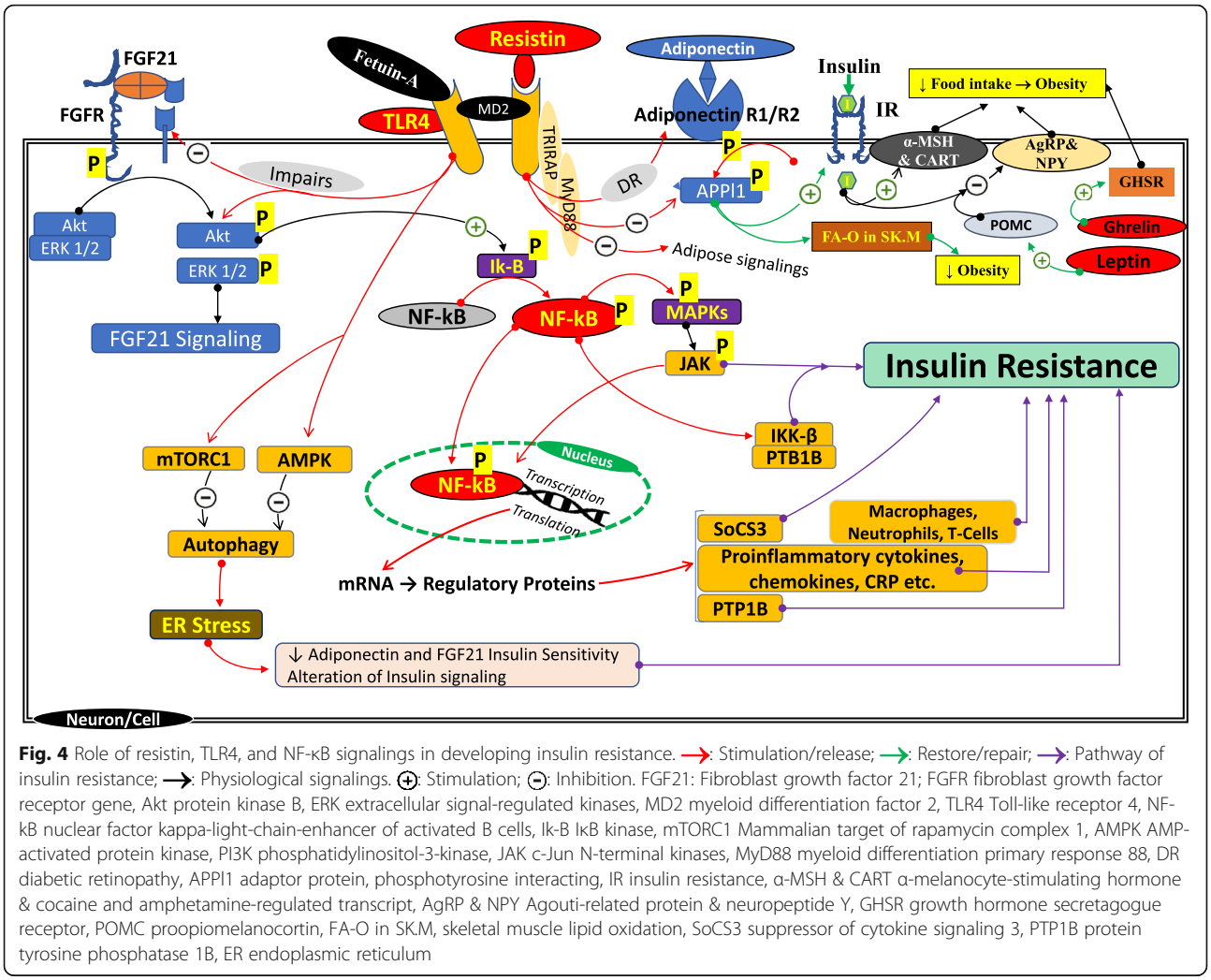

Fig. 4 Role of resistin, TLR4, and NF-κB signalings in developing insulin resistance. →: Stimulation/release; →: Restore/repair; →: Pathway of insulin resistance; →: Physiological signalings. ⊕: Stimulation; ⊖: Inhibition. FGF21: Fibroblast growth factor 21; FGFR fibroblast growth factor receptor gene, Akt protein kinase B, ERK extracellular signal-regulated kinases, MD2 myeloid differentiation factor 2, TLR4 Toll-like receptor 4, NF-kB nuclear factor kappa-light-chain-enhancer of activated B cells, Ik-B IκB kinase, mTORC1 Mammalian target of rapamycin complex 1, AMPK AMP-activated protein kinase, PI3K phosphatidylinositol-3-kinase, JAK c-Jun N-terminal kinases, MyD88 myeloid differentiation primary response 88, DR diabetic retinopathy, APPl1 adaptor protein, phosphotyrosine interacting, IR insulin resistance, α-MSH & CART α-melanocyte-stimulating hormone & cocaine and amphetamine-regulated transcript, AgRP & NPY Agouti-related protein & neuropeptide Y, GHSR growth hormone secretagogue receptor, POMC proopiomelanocortin, FA-O in SK.M, skeletal muscle lipid oxidation, SoCS3 suppressor of cytokine signaling 3, PTP1B protein tyrosine phosphatase 1B, ER endoplasmic reticulum

creation and expansion of hypothalamic insulin resistance [63]. The elevated NF-κB signaling in HFD animal models activates the mTORC1, leading to ER (endoplasmic reticulum). This triggers insulin resistance in hypotheses accelerates the obesity and type 2 diabetes progression [64]. Prolonged ER stress leads to increased buildup of stretched protein response which involves insulin resistance and inflammation in the hypothalamus [65].

Fascinatingly, the deficiency of PTP1B in mice improved insulin sensitivity in the central hypothermic region and reduced the progression of obesity and related metabolic complications [66]. TLR family protein (TLR4) also contributes to hypothalamic inflammation (HI) and IR [67]. TLR4 is the main component and target of saturated FAs in the hypothalamus and peripheral tissues that further release the pro-inflammatory mediators, thus triggering the insulin resistance and ER stress in the entire body [67].

Recent findings have reported elevated levels of Fetuin-A, a glycoprotein (TLR4 ligand) released by hepatocytes and adipose cells. Fetuin-Ais needed for FF-dependent activation of TLR and facilitates inflammation and IR. TLR4 inhibition in mice protected HFD-induced IR and inflammation [68]. The co-factor protein, myeloid differentiation factor (MyD88) is a downstream mediator for TLR4 pathways in mice, and its reduced levels defended HFD-induced obesity, blood glucose intolerance, and peripheral insulin resistance [69].

Furthermore, some reports have specified that TLR4-mediated microglia signaling pathways also have a central part in the control of ARC neural activity and feeding behavior [70]. Finally, this information strongly indicates that the TLR4 path plays a significant role in the progression of overweight, inflammation, and IR. This problem also might be varying with diet variations. The TLR4 is also involved in breast cancer progression [71]. Recent reviews have stated that resistin may

potentiate the inflammation and IR by activating PLR4 and its downstream pathways, which promote central, peripheral insulin resistance, and inflammation [72].

The resistin released from the adipose tissue in rodents and macrophages in humans can encourage the release of inflammatory mediators and worsen inflammation and IR [73]. Resistin impairs peripheral insulin responsiveness [72], whereas the absence or lack of resistin or administration of antibodies against resistin improved sensitivity to insulin [74], and some reports have described incompatible results [75]. Apart from this contradiction, the resistin has a key role in the invention of pro-inflammatory agents (TNFα, LI-6, via NF-κB), which are generally involved in peripheral IR in animal models and the humans [76].

Resistin accelerates pro-inflammatory agents (TNFα, LI-6, via NF-κB), leading to deep alterations in insulin signaling mechanisms and worsening of IR [77]. Resistin also presents in the hypothalamus and regulates the inflammation in CNS [72], which has modulatory action on neurons and regulates glucose, food consumption, and lipid metabolism. This suggests that resistin has a regulatory role in obesity and IR [77], but the information about resistin-inducing hypothalamic inflammation and its receptors is not well documented.

Resistin may alter insulin receptors, AKT, and ERK1/2 protein phosphorylation in the brain [69]. This might lead to the stimulation of SOCS-3 and PTP1B (negative insulin signaling modulators) [78]. It can also activate JNK and p38 MAPK, which promotes the serine phosphorylation of IRS1. This further increase insulin resistance [60] and another proposed mechanism of resistin-causing hypothalamic inflammation and IR via impairment of adiponectin and FGF21 signaling called as insulin-sensitizing hormones [79]. Resistin treatment decreases adiponectin receptors expression centrally [69]. This protein might be mixed up in adipose-Rs signaling, which contributes to the insulin-sensitizing effect of adiponectin and also diminished FGF21 and its receptors (FGFR1 and KLB) in the hypothalamic region. This further involves the impairment of FGF21 and adiponectin signals in both humans' and animals' (mouse) neural cells [69].

The overexposure of resistin can decrease autophagy via suppression of many autophagy markers like LC3, ATG7, and Beclin1 [80]. This can occur by activating the TLR4 which leads to inhibition of phosphorylation of AMPK and stimulation of Akt/mTOR, which regulates autophagy. In specific, resistin decreased the level of LC3 in the arcuate nucleus through TLR4 signaling [80]. This suggests that resistin/TLR4 or both regulate the neural autophagy and might be a part of inflammation and insulin resistance in the hypothalamic region. This observation is remarkable about HFD-induced stimulation of astrocytes and microglia that are crucially involved in inflammation and IR in the hypothalamic region [81].

3 Conclusion

Obesity plays a vital key role in the development of central and fringe insulin resistance leading to type 2 diabetes. The resistin, TLR4, and NF-κB signaling mechanisms promote the central inflammation and insulin resistance.

The HFD-STZ diabetic model has become more popular for the assessment of new phytochemicals against type 2 diabetic complications. In this combination, the HFD develops obesity and insulin resistance (IR) and the streptozotocin can cause an insulin shortage by DNA fragmentation and induce oxidative stress in the β cells by accelerating the invention of ROS like hydroxyl, nitrogen oxide, hydrogen peroxide, and oxygen.

NF-κB is a crucial pathway in the pathogenesis of various macro- and micro-level diabetic complications. Inhibition of the NF-κB signaling cascade may provide an effective clinical correlation for diabetes to prevent complications. Although various natural, synthetic, and semi-synthetic NF-κB inhibitors are available, their clinical considerations are limited. Based on this review, it can be concluded that the resistin, TLR4, and NF-κB signaling pathways are highly focused and are the vital future targets for overcoming the central, fringe changes, and effective treatment of diabetic vascular complications.

Abbreviations

ADP: Adenosine diphosphate; AGEs: Advanced glycation end products; AgRP & NPY: Agouti-related protein & neuropeptide Y; Akt: Protein kinase B; AMPK: AMP-activated protein kinase; APPI1: Adaptor protein, phosphotyrosine interacting; ARase: Aldose reductase; AT-II: Angiotensin II; ATP: Adenosine triphosphate; ATP: Adenosine tri-phosphate; Bcl-2: B cell lymphoma 2; BG: Blood glucose; BGL: Blood glucose level; BP: Blood pressure; CAM: Cellular adhesion molecule; COX-2: Cyclooxygenase-2; CYP: Cytochrome P450; DAG: Diacylglycerol; DN: Diabetic nephropathy; DNA: Deoxyribonucleic acid; eNOS: Endothelial NOS; ER: Endoplasmic reticulum; ERK: Extracellular signal-regulated kinases; ET-1: Endothelin 1; FGF21: Fibroblast growth factor 21; FGFR: Fibroblast growth factor receptor gene; GHSR: Growth hormone secretagogue receptor; GLUT2: Glucose transporter 2; GSH: Glutathione; HbAc1: Glycated hemoglobin; HFD: High-fat diet; ICAM: Intercellular adhesion molecule; Ik-B: IκB kinase; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-8: Interleukin-8; iNOS: Inducible nitric oxide synthase; IR: Insulin resistance; IR: Insulin resistance; JNK: c-Jun N-terminal kinase; KLB: β-Klotho gene; LC3: Light chain 3; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; MD2: Myeloid differentiation factor 2; mTORC1: Mammalian target of rapamycin complex 1; MYD88: Myeloid differentiation primary response 88; NAD: Nicotinamide adenine dinucleotide; NADPH: Nicotinamide adenine dinucleotide phosphate; NCV: Nerve conduction velocity; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NGF: Nerve growth factor; NO: Nitric oxide; PI3K: Phosphatidylinositol-3-kinase; PKC: Protein kinase C; POMC: Proopiomelanocortin; PTP1B: Protein tyrosine phosphatase 1B; RAGE: Receptor for advanced glycation endproducts; ROS: Reactive oxygen species; SoCS3: Suppressor of cytokine signaling 3; STZ: Streptozotocin; TG: Triglycerides; TLR: Toll-like receptor 4; TNF: Tumor necrosis factor beta; TNF-α: Tumor necrosis factor-alpha; VEGF: Vascular endothelial growth factor; XO: Xanthine oxidase; ZDF: Zucker diabetic fatty; α-MSH & CART: α-Melanocyte-stimulating hormone & cocaine and amphetamine-regulated transcript

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Authors' contributions
VG performed all the research activities, writing, and design. BC conceived the study and participated in its design and coordination. The authors have read and approved the manuscript.

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Competing interests
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