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Breakthroughs and Views

Is NF-κB a culprit in type 2 diabetes?

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Abstract

It has been generally viewed that salicylates ameliorate type 2 diabetes through interfering with the NF-κB signaling. Earlier studies indicated that IKKβ was the key for the development of insulin resistance. However, it was unknown whether IKKβ itself, or its downstream target, NF-κB, plays major roles in insulin resistance. New data suggest that NF-κB and NF-κB-regulated cytokines are crucial for the diabetogenesis.
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NF-κB is arguably the most important transcription factor for the initiation or progression of numerous human diseases [1,2]. As a ubiquitous transcription factor governing the expression of viruses or a variety of inflammatory cytokine genes, NF-κB was first implicated in the pathogenesis of human immunodeficiency virus-1 (HIV-1) infection [3]. Further studies suggest that activation of NF-κB is responsible for the pathological progress of neurological disorders, carcinogenesis, immune deficiency, rheumatoid arthritis, atherogenesis, Crohn's disease, cystic fibrosis, asthma, osteopetrosis, ischemic reperfusion, etc. [4].

Recent studies have highlighted the role of NF-κB in the development of insulin resistance and type 2 diabetes [5–7]. However, evidence for the involvement of NF-κB in insulin resistance is not new. The earliest indication of the contribution of this transcription factor to diabetes can be traced back even far before the discovery of NF-κB. Clinicians as well as researchers in the diabetes field have been puzzled for more than one century by the ameliorating effect of high dose salicylates on hyperglycemia in type 2 diabetes [8]. The milestone discovery that salicylates, including sodium salicylate and aspirin, mainly targeted NF-κB and its upstream kinase, IKKβ, for their pharmaceutical effect of anti-inflammation brought NF-κB as a chief suspect for the development of insulin resistance and type 2 diabetes [9,10]. A sustained activation of NF-κB by hyperglycemia has been observed in several experimental systems [11,12]. In bone marrow-derived mesenchymal cells, activation of NF-κB antagonizes the function of PPARγ [13], a prototypical nuclear receptor that regulates lipid and glucose homeostasis [14]. Tumor necrosis factor-α (TNFα), a NF-κB-regulated product as well as a potent activator of NF-κB, induces insulin resistance predominantly through the serine phosphorylation of insulin receptor substrate-1 (IRS1) [15,16]. TNFα was highly induced in the adipose tissues of obese animals and human subjects [17,18]. In experimental animals, neutralization of TNFα increases insulin sensitivity [15], although such treatment failed to improve insulin resistance in obese human subjects [19].

The most compelling evidence linking NF-κB with type 2 diabetes is provided by Shoelson's group who studied the heterozygous deletion of Ikkβ gene ($Ikk\beta^{+/-}$) and insulin resistance in mice in 2001 [5]. IKKβ is the main subunit of the IKK complex in mediating

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proinflammatory signal-induced phosphorylation of NF-κB inhibitor, IκBα, leading to the degradation of IκBα and the consequent activation of NF-κB. Mice with homozygous deletion of Ikkβ (Ikkβ$^{-/-}$) died in utero because of severe liver apoptosis, whereas heterozygous Ikkβ$^{+/-}$ mice appear to be normal [20,21]. Reduced Ikkβ gene dose by disrupting a single Ikkβ allele was able to correct both the skeletal insulin resistance and the biochemical defects in IRS1 tyrosine phosphorylation in obese animals [5]. Nevertheless, it was unknown at that time whether IKKβ directly affected the process of insulin resistance, such as serine/threonine phosphorylation of IRS1, or indirectly participated in this process through its downstream target, NF-κB. Considering the number of serine/threonine residues in IRS1, it was very likely that IKKβ might promote IRS1 phosphorylation through broad cross-talking kinases. Indeed, a number of studies had documented that JNK was the key kinase for the serine/threonine phosphorylation of IRS1 in response to high fat diet, obesity or endoplasmic reticulum stress [22,23].

Further evidence supporting the involvement of NF-κB, rather than IKKβ itself, in the insulin resistance is provided by two most recent independent studies of the selective transgenic expression or knockout of Ikkβ in the liver [6,7]. Overexpression of Ikkβ in the liver, which causes sustained activation of NF-κB as seen in chronic liver inflammation, substantiates high fat diet- or obesity-induced insulin resistance. Conversely, attenuation of NF-κB activation by co-expression of IκBα in the liver not only diminished the expression of NF-κB-dependent genes, but reversed the phenotypes of type 2 diabetes also [6]. Systemic neutralization of IL-6 exhibited a significant improvement in insulin resistance in the mice with transgenic liver expression of Ikkβ [6]. Similarly, administration of IL-1 receptor antagonist, a specific inhibitor of IL-1 signaling, improved the inflammation-induced hyperglycemia significantly [7]. Thus, these results clearly suggested that NF-κB and its target genes, such as TNFα, IL-1, and IL-6, are critical in the development of insulin resistance.

Now it appears to be unequivocal that NF-κB is a culprit in the development of insulin resistance and the diabetic complications. However, there are still many unanswered questions. First and foremost, it is uncertain whether the extreme insulin resistance induced by chronic liver inflammation in rodent models correlates with the human type 2 diabetes that largely resulted from obesity [24]. There is as of yet no evidence indicating that chronic liver inflammation is the main factor for the epidemic of type 2 diabetes. Second, a sustained activation of NF-κB has been observed in the mononuclear cells from the patients with type 1 diabetes [25]. No such observation was made in patients with type 2 diabetes. The contribution of NF-κB to the human type 2 diabetes remains to be examined. Third, the main features of insulin resistance are characterized by the decreases in insulin receptor and its kinase activity, impairment in tyrosine phosphorylation of IRS1 or IRS2, abnormality in glucose transporter translocation, and the alterations in the activities of a number of intracellular glucose metabolic enzymes [26,27]. We do not know which part in these insulin signaling pathways is affected by the NF-κB-regulated inflammatory genes. Earlier studies suggested that the insulin resistance induced by TNFα was largely due to the serine phosphorylation of IRS1, resulting in reduction of tyrosine phosphorylation and the subsequent PI3K association of the IRS1 [16,18]. It is unknown whether other NF-κB-regulated cytokines, such as IL-6 and IL-1, achieve their diabetogenic effect through the same mechanism. Fourth, all of these so-called NF-κB inducers in these experimental insulin resistance models, including hyperglycemia, TNFα, free fatty acids, etc., are also capable of activating a number of other kinases, such as MAPK, PI3K, Akt, PKCs, and JAK/STAT. The exact roles of these kinases in insulin action are unclear [28]. Finally, insulin resistance can be attributed, at least in part, to the sustained activation of IKKβ and its downstream transcription factor, NF-κB. However, a careful assessment should be made of the potential beneficial effects of targeting this pathway to sensitize the insulin signal. As a key survival transcription factor [4,29], NF-κB may be pivotal for compensatory expansion of β-cell mass in islets during the loss of insulin sensitivity [30]. NF-κB has also been implicated as an essential transcription factor for the β-cell expression of Glut2 that contributes to the glucose-stimulated insulin secretion by β-cells [31]. Suppression of this transcription factor, therefore, may have deleterious effects on insulin resistance and type 2 diabetes.

The biggest challenge faced by our society and scientists today is that more than 150 million people are living with type 2 diabetes worldwide [32]. Despite dramatic improvements in the drug therapy, a chilling fact is that the epidemic will continue to expand in the next 20 years. The projected number of people who suffer from type 2 diabetes will be about 300 million in 2025 [32]. The current therapeutic paradigm for type 2 diabetes relies mainly on the reduction of hyperglycemia, interfering with gut glucose absorption and the augmentation of glucose utilization by peripheral tissues [33]. The development of thiazolidinedione (TZD) drugs, agonists of peroxisome proliferators-activated receptor-γ (PPARγ), sparked a tide of optimism among researchers and people with this disease several years ago [14]. Unfortunately, the limited efficacy and considerable side effects of the traditional and the TZD drugs have compromised the clinical application of these drugs. Thus, a new therapeutic strategy based on the defined molecular mechanism of type 2 diabetes is critically needed. Certainly, elucidation of the IKKβ-NF-κB

involvement in insulin resistance and type 2 diabetes may provide a conceptual framework for identifying novel therapeutic targets of this disease.

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