Endothelial Nuclear Factor κB in Obesity and Aging

Is Endothelial Nuclear Factor κB a Master Regulator of Inflammation and Insulin Resistance?

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Insulin resistance is a major characteristic of type 2 diabetes mellitus and develops in multiple organs, including skeletal muscle, liver, adipose tissue, and heart. Insulin resistance is caused by obesity and therefore establishes an important causal relationship between obesity and type 2 diabetes mellitus. Insulin resistance also develops in aging, but this process is less well understood. Obesity is a complex physiological state, with alterations in lipid metabolism, dysregulated production of hormones, ectopic accumulation of fat, mitochondrial dysfunction, and chronic low-grade inflammation. All of these abnormalities may independently cause insulin resistance and affect glucose homeostasis, which make insulin resistance equally as complex as obesity itself.

Nuclear factor κB (NF-κB) is a complex of transcription factors that regulate cytokine gene expression and the inflammatory response. NF-κB is normally sequestered in the cytoplasm by inhibitory proteins (IκB) and becomes activated in response to various stimuli (eg, tumor necrosis factor-α, lipopolysaccharide, fatty acids) when IκB is phosphorylated by IκB kinase-β and degraded, leading to nuclear translocation of NF-κB. It is clear that NF-κB plays a major role in obesity-induced inflammation and insulin resistance as evidenced by mechanistic and therapeutic findings. Toll-like receptor signaling is stimulated by fatty acids and mediates NF-κB activation and inflammatory response in obese animals. Liver-selective activation of NF-κB increases hepatic production of proinflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-6, and IL-1β, and causes insulin resistance in mice. Proinflammatory cytokines exert endocrine and paracrine effects to activate stress kinase signaling and downregulate insulin signaling in skeletal muscle and liver. Conversely, chronic treatment of high-dose aspirin and salicylate, which are potent inhibitors of NF-κB and inflammation, improves insulin sensitivity in diabetic humans and animal models. Anti-inflammatory cytokine, IL-10, also prevents insulin resistance in obese animals. Thus, NF-κB is a molecular link to obesity, inflammation, and insulin resistance (Figure 1).

In this issue of Circulation, Hasegawa and colleagues examined the role of endothelial NF-κB signaling in obesity and aging-associated metabolic abnormalities by the use of transgenic mice expressing dominant-negative IκB under the Tie2 promoter/enhancer (E-DNIκB mice). Young E-DNIκB mice were more insulin sensitive than wild-type littermates based on hyperinsulinemic-euglycemic clamps. After 20 weeks of high-fat feeding, E-DNIκB mice became obese indistinguishable from the wild-type mice, but they became less insulin resistant based on glucose/insulin tolerance tests. When E-DNIκB mice were crossed with genetically obese (A2+/+) mice, E-DNIκB;A2/+ mice were more insulin sensitive than A2+/+ mice, despite marked obesity in both groups of mice. These beneficial effects of endothelial inhibition of NF-κB were associated with reduced aortic expression of adhesion molecules (vascular cell adhesion molecule-1, E-selectin) and antioxidative enzymes and upregulation of endothelial nitric oxide synthase signaling. In adipose tissue of E-DNIκB;A2/+ mice, there were less macrophage infiltration and inducible nitric oxide synthase expression than in A2/+ mice. In skeletal muscle, blood flow and markers of mitochondrial biogenesis and function were all elevated in E-DNIκB;A2/+ mice in comparison with insulin-resistant A2/+ mice, which is consistent with higher locomotor activity in E-DNIκB;A2/+ mice. Essentially, endothelial inhibition of NF-κB improved insulin resistance and glucose homeostasis in diet-induced or genetically obese mice.

Why are these findings of Hasegawa and colleagues important when NF-κB–targeted diabetes therapy was in use 100 years ago, and salsalate, a nonacetylated prodrug of salicylate, is already showing promising clinical trial results? The answer can be found in the following scenario of a potential paradigm shift. The early paradigm on the role of inflammation in obesity-induced insulin resistance is adipocentric. It primarily involves adipose tissue inflammation with massive infiltration of macrophages and local production of proinflammatory cytokines under obese conditions. Adipocyte-derived tumor necrosis factor-α, IL-6, IL-1β, and possibly other cytokines are then released into circulation and activate stress kinase signaling (eg, c-Jun N-terminal kinase) in liver and skeletal muscle to induce insulin resistance in these organs. Accordingly, adipose-selective deletion of c-Jun N-terminal kinase 1 inhibits adipocyte production of IL-6 in response to diet-induced obesity and prevents hepatic insulin resistance in mice. However, this paradigm has important gaps. Insulin resistance in skeletal muscle and liver develops in early obesity.

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but measurable adipose tissue inflammation does not develop until the late stage of obesity (after 16–20 weeks of high-fat feeding). Furthermore, circulating levels of proinflammatory cytokines are not markedly elevated until the late stage of obesity. In this regard, increasing evidence suggests that inflammation and macrophage activation occur in nonadipose tissues in obesity. Indeed, increased activation of Kupffer cells in liver and elevated macrophage accumulation in skeletal muscle, islets, heart, and brain have been reported in obese animals. In light of these recent findings and the current findings of Hasegawa and colleagues, the adipocentric paradigm needs to be reexamined in the context of endothelial NF-κB regulation of local inflammation and macrophage-derived cytokines that may directly induce insulin resistance via paracrine effects in individual organs (Figure 2).

Moreover, these findings also suggest that obesity-associated inflammation may be a global event that develops in multiple organs and cell types. In that regard, the endothelial cells line the entire circulatory system, extending to every organ in the body, and are the first line of contact with blood (or blood-borne substances). The current findings of Hasegawa and colleagues further implicate that obesity-induced activation of endothelial NF-κB may be an important signal for systemic inflammation and macrophage infiltration into multiple metabolic organs. This notion is supported by their findings that adipose tissue inflammation is markedly suppressed and skeletal muscle remains metabolically active in obese E-DNI-κB mice. However, important questions remain unanswered. Is inflammation in nonadipose organs, such as liver, skeletal muscle, and islets, attenuated in E-DNI-κB mice? What are the major stimuli for activation of endothelial NF-κB?
NF-kB in obesity? It will also be important to examine the effects of inhibiting endothelial NF-kB on local inflammation and insulin resistance in early-stage obesity.

In addition to protection from obesity-mediated insulin resistance, E-DNIkB mice were also rescued from aging-associated insulin resistance and hypertension. Fifty-week-old E-DNIkB mice were more insulin sensitive and showed lower systolic blood pressure than age-matched wild-type mice. Because endothelial inhibition of NF-kB increased endothelial nitric oxide synthase expression and skeletal muscle blood flow, these events coupled to vasodilation may underlie the observed blood pressure effects. In fact, these findings rehash the old notion on the role of blood flow in insulin resistance and blood pressure.24 In that case, is it possible that aging-associated insulin resistance is mediated by reduced skeletal muscle blood flow secondary to hypertension? This should be examined further, because we know very little about how aging causes insulin resistance. Remarkably, endothelial inhibition of NF-kB prolonged life spans with nearly a 20% increase in longevity in E-DNIkB mice in comparison with wild-type mice. These effects were associated with reduced vascular senescence and oxidative stress markers, but increased muscle blood flow and activity in E-DNIkB mice. These beneficial effects of endothelial NF-kB inhibition resemble the antiaging effects of sirtuins, which remain controversial.25 It will be important to determine whether longevity in E-DNIkB mice is causally associated with the beneficial effects on insulin sensitivity, mitochondrial function, and/or cardiovascular function.

It has been >25 years since Sen and Baltimore’s breakthrough discovery of NF-kB as a master regulator of cellular response to inflammation and stress.26 As we are beginning to understand type 2 diabetes mellitus as an inflammatory disease, NF-kB in endothelium, as described in this issue of Circulation, has a renewed role to potentially treat a century-old disease.

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Disclosures
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References
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