Metabolic Syndrome: Is Nlrp3 Inflammasome a Trigger or a Target of Insulin Resistance?

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The NLRP3 Inflammasome Instigates Obesity-Induced Inflammation and Insulin Resistance
Vandanmagsar et al
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The Nlrp3 inflammasome has recently been implicated in the development of the metabolic syndrome through the impairment of adipose tissue insulin sensitivity. Recent literature associates Nlrp3 activation with much pathology caused by prolonged insulin resistance state, therefore establishing Nlrp3 as a promising therapeutic target for type-2-diabetes treatment.

More than 27% of the U.S. population suffers from the metabolic syndrome,[1] which includes several of our most common health problems, such as central obesity, glucose intolerance/type 2 diabetes, dyslipidemia with accelerated atherosclerosis, hypertension, nonalcoholic hepatosteatosis, and elevated uric acid with increased risk of gout.[2] Despite the varied clinical presentation, many of the components of the metabolic syndrome are driven by one single etiologic factor—insulin resistance.[3,4] Indeed, mouse models with insulin resistance in various tissues have been shown to mimic many aspects of the metabolic syndrome.[5,6]

Despite the growing body of evidence that demonstrates the importance of diet and obesity to the onset of insulin resistance and the metabolic syndrome, the molecular mechanisms underlying this phenomenon are not completely understood. Inflammation at the level of adipose tissue and liver,[7–9] oxidative stress,[10] and mitochondrial dysfunction[11] have all been shown to promote insulin resistance. However, how these act to give rise to the multifactorial pathophysiology of insulin resistance and how alterations in the energy balance can be sensed by cells of the organism and translated into signals that could affect insulin sensitivity are not known.

In a recent report, Vandanmagsar et al[12] demonstrate that danger signals originating with obesity are sensed by the Nlrp3 class of cytosolic pattern recognition receptors, which

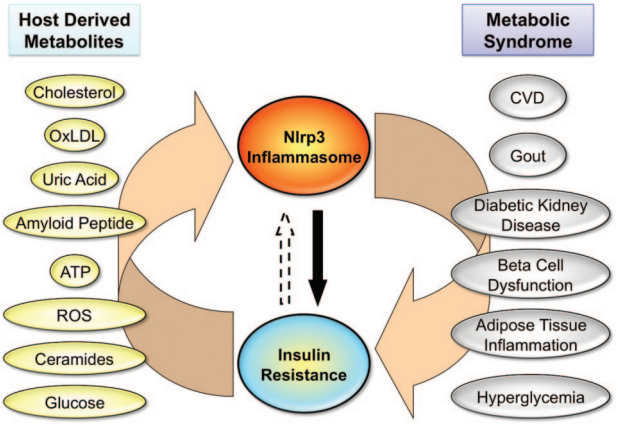

Figure. Cross-talk between insulin resistance and Nrlp3 inflammasome. OxLDL indicates oxidized low density lipoprotein; ATP, adenosine triphosphate; ROS, reactive oxygen species; CVD, cardiovascular disease.

are expressed in cells involved in the innate immune response, such as macrophages, and can activate a proinflammatory response mediated by interleukin (IL)-1α that results in insulin resistance at the level of fat, liver, and muscle of obese animals. Different from other pattern recognition receptors in the immune system, which are responsive to pathogen-derived antigens, the Nlrp3 inflammasome can be activated by host-derived molecules that are abundant in obese individuals, including excess ATP, glucose, ceramides, reactive oxygen species, oxidized LDL, uric acid, as well as crystals of cholesterol.[13] Activation of the Nlrp3 inflammasome by these endogenous signals results in caspase-1–mediated processing and activation of IL-1α in macrophages.[13] This promotes classical M1 activation of macrophages that has been linked to the development of inflammation in adipose tissue and metabolic diseases.[14,15]

These investigators further demonstrated that mice with ablation of the Nlrp3 receptor are resistant to diet-induced insulin resistance and hepatosteatosis and that this correlates with reduced activation of T cells in adipose tissue. They also showed that macrophages from the adipose tissue of Nlrp3 knockout mice have a blunted response to ceramide, which may explain the reduced M1 polarization of macrophages in the fat tissue in response to obesity. These findings suggest that the Nlrp3 inflammasome is a missing piece in the puzzle of the complex mechanisms involved in the onset of the metabolic syndrome and could be a potential target for treatment of insulin resistance.

Interestingly, the sulfonylurea glyburide—an anti-diabetic drug that stimulates insulin secretion—has recently been shown to act as an inhibitor of Nlrp3.[16] More importantly, therapeutic agents that block IL-1α signaling improve glyce-

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mic control of diabetic patients, demonstrating that targeting the Nlrp3 inflammasome is a promising therapeutic strategy in type 2 diabetes clinical trials.[17]

With this in mind, the next obvious question is whether manipulating the Nlrp3 inflammasome may also affect other components of the metabolic syndrome? Even though the answer to this question is not clear, there is a growing body of evidence that supports a potential role of the Nlrp3 inflammasome in the development of multiple aspects of the metabolic syndrome. As noted by Vandanmagsar et al, the Nlrp3 inflammasome is activated in adipose tissue in mouse models of obesity and attenuated by calorie restriction. It also correlates with glycemia in type 2 diabetes patients after weight loss interventions.[12] Reactive oxygen species and mitochondria dysfunction in adipose tissue, which have been implicated in the cellular stress cascades leading to insulin resistance, are activating signals of the Nlrp3 inflammasome.[18] Others have shown that islet amyloid polypeptide in diabetic pancreas can activate Nlrp3 inflammasome and induce IL-1α secretion and inflammation of the islets, leading to the development of pancreatitis.[19] Crystalline cholesterol present in atherosclerotic lesions has also been shown to be a potent activator of Nlrp3, thereby participating in the inflammatory process present in atherosclerotic plaques.[20] Two recent genome-wide association studies have identified associations between SNPs in the Nlrp3 gene with high circulating levels of C-reactive protein and fibrinogen, two predictors of coronary heart disease.[21,22] Uric acid crystals involved in gout are also capable of activating Nlrp3.[23] Moreover, uric acid and IL-1α levels are both correlated with osteoarthritis progression and pathology,[24] suggesting a role of the Nlrp3 inflammasome. Finally, in diabetic nephropathy, local IL-1α secretion has been shown to participate in the onset of kidney inflammation, and Nlrp3 inflammasome activation is observed in chronic kidney disease.[25,26]

Despite the potential role of the Nlrp3 inflammasome in metabolic syndrome, activation of this pathway in fat occurs late in obesity (7 months from the beginning of the high-fat diet in the mouse), suggesting that the Nlrp3 inflammasome is not a primary etiologic factor in the disease.[12] In fact, many other pathways have been shown to promote insulin resistance and the metabolic syndrome before activation of caspase-1 and IL-1α during obesity. These include the numerous pathways known to induce recruitment of T cells and activation of macrophages in adipose tissue and liver[7–9] and alterations in insulin receptor levels and insulin signaling through its receptor and substrate proteins.[27] It is also not clear if the most common danger signals that are elevated with obesity, such as changes in nutrient metabolism,[28,29] mitochondria dysfunction,[11] and endoplasmic reticulum stress[10,30] require the Nlrp3 inflammasome to promote insulin resistance. It also remains to be determined if insulin resistance itself can activate the Nlrp3 inflammasome, therefore creating one of many vicious cycles involved in the insulin resistance/inflammation axis.

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