INSULIN RESISTANCE IS A LEADING CAUSE of type 2 diabetes, and inflammation has emerged as an important mediator between obesity and insulin resistance. The links between immunity and metabolism are extensive and have been proposed to originate from structures in lower organisms that are responsible for both danger and metabolite sensing (6). This has introduced the interesting concept that commonly ingested foods and/or metabolites may engage pattern recognition receptors (PRRs) of the immune system and represent a form of host-pathogen sensing. Indeed, innate immune PRRs, such as Toll-like receptors (TLRs), have been implicated in the inflammation induced by saturated fatty acids (7, 10). Conversely, more widely recognized host-pathogen interactions, such as bacterial lipopolysaccharide (LPS)-induced TLR4-mediated inflammation, have been implicated in insulin resistance. In particular, LPS acting directly on muscle reduces fatty acid oxidation (5).

Importantly, metabolic endotoxemia is associated with obesity, and a low-level chronic elevation in LPS is sufficient to elicit insulin resistance (2, 5). Penetration of microbial products from the gut lumen into the circulation regulates systemic immunity (8), and changes in the gut flora have been implicated in metabolic endotoxemia-associated insulin resistance (3).

Identifying the specific immune components that are engaged by dietary and environmental factors underlying obesity-induced inflammation may yield avenues of therapeutic intervention for insulin resistance (3). Among PPRs, the nucleotide oligomerization domain (NOD)1 and -2 proteins are intracellular sensors of bacterial cell wall peptidoglycan (PGN) moieties, which induce stress and inflammation pathways. NOD1 detects PGN structures typically found in gram-negative bacteria, whereas NOD2 recognizes PGN segments more abundant in gram-positive strains. Intriguingly, NOD1 sensing of microbiota-derived PGN, but not TLR4, has been directly implicated in priming certain immune responses (4).

Recent evidence has now connected NOD1- and NOD2-activating bacterial motifs with insulin resistance. In the current issue, Zhao et al. (14) demonstrate that administration of a PGN-based NOD1 activator to adipocytes activates inflammatory programs, impairs insulin signaling, and decreases insulin-stimulated glucose uptake. That paper also shows that human primary adipocytes respond to NOD1 ligand by inducing expression of inflammatory mediators. These results are important, because adipose tissue is increasingly recognized as a key site of inflammation that can propagate responses leading to systemic insulin resistance. On the other hand, we recently showed that PGN motifs that act on NOD2, but not those acting on NOD1, induce muscle cell-autonomous insulin resistance (11). These results point to an intriguing cell type-linked discernment of NOD1 and NOD2 ligands, in each case resulting in impaired insulin action.

Expanding on this in vitro evidence, we recently showed that NOD1-activating bacterial PGN motifs causes acute systemic insulin resistance in mice (9). Such NOD1 activation potently suppressed insulin action in the liver, as revealed by hyperinsulinemic euglycemic clamps. Moreover, NOD1 ligands directly suppressed insulin action in isolated hepatocytes and, concordant with the findings from Zhao et al., NOD1 ligands decreased insulin-mediated glucose uptake directly in adipocytes (9). Hence, one may conclude that NOD1 ligand-mediated peripheral insulin resistance, which indirectly manifested in skeletal muscle, appears to involve complex cell/tissue cross talk, likely from hepatic and adipose tissue. Conversely, NOD2-activating bacterial PGN motifs caused a milder insulin resistance in vivo that affected skeletal muscle preferentially (Fig. 1).

There appear to be many parallels in NOD1-adipocyte/hepatocyte- and NOD2-myocyte-mediated insulin resistance, including activation of MAPKs (p38, JNK, ERK1/2), expression and production of proinflammatory cytokines/chemokines, and impairments in insulin signaling at the level of IRS-1. In each case, it is unknown whether intracellular stress kinase activation or autocrine actions via secretion of proinflammatory mediators are the primary mediators of insulin resistance.

Fig. 1. Intracellular pattern recognition receptors (PPR) nucleotide oligomerization domain (NOD)1 and NOD2 link innate immunity to insulin resistance. NOD1 activation by meso-DAP peptidoglycan (PGN) characteristic of gram-negative bacteria elicits liver and adipose insulin resistance. NOD2 activation by Lys PGN, which predominates in gram-positive bacteria, decreases insulin resistance directly in skeletal muscle. NOD1 affected targets and then indirectly impaired insulin action in muscle.


