

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart
Association® 
Learn and Live™

Innate Immune Pathway Links Obesity to Insulin Resistance

Prediman K. Shah

Circ. Res. 2007;100;1531-1533

DOI: 10.1161/CIRCRESAHA.107.101104

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2007 American Heart Association. All rights reserved. Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circres.ahajournals.org/cgi/content/full/100/11/1531>

Subscriptions: Information about subscribing to Circulation Research is online at
<http://circres.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Innate Immune Pathway Links Obesity to Insulin Resistance

Prediman K. Shah

The prevalence of obesity, especially among adolescents, has increased considerably over the past 20 years because of increased caloric intake and reduced physical activity. It has been estimated that 20% of the world's population is overweight and nearly 300 million are obese (BMI >30 kg/m²).^{1,2} Excess body weight and obesity are associated with the development of metabolic syndrome and type II diabetes, both of which are associated with insulin resistance and increased risk of cardiovascular complications.^{1,2}

Atherothrombotic vascular disease, resulting from a complex interplay between dyslipidemia and vascular immunoinflammatory processes, is responsible for a majority of the excess morbidity and mortality that characterizes metabolic syndrome and type II diabetes.^{1,2} Several studies have shown that obesity is associated with activation of inflammatory pathways and that inflammatory responses are associated with impaired insulin signaling and insulin resistance.^{3–8} Considerable progress has been made in the last 2 decades in our understanding of molecular events that link obesity to inflammation, insulin resistance, type II diabetes, and enhanced vascular disease. Obesity-mediated skeletal muscle insulin resistance has been linked to defects in cellular signaling events triggered by insulin.^{3–8} In obesity, the skeletal muscle levels of several kinases such as protein kinase C isoforms (PKC), I Kappa B Kinase- β (IKK- β), and c-jun-terminal kinase (JNK) are elevated, and these kinases have been implicated in suppression of insulin signaling by promoting serine phosphorylation of insulin receptor substrate (IRS) which is associated with suppression of tyrosine phosphorylation of IRS (Figure).¹ Several studies have shown that nutrient excess and obesity are associated with elevated levels of circulating free fatty acids, and the elevated levels of free fatty acids can induce insulin resistance in peripheral tissues such as muscle and liver by disrupting insulin signaling; in part through PKC epsilon-mediated downregulation of insulin receptor (IR) gene.^{3–10} Recent studies have demonstrated that free fatty acids lead to activation of the innate immune receptor, Toll-like receptor 4 (TLR-4), and the downstream proinflammatory transcription factor NF- κ B

which may play an important role in mediating inflammation and insulin resistance.⁹

In this issue of *Circulation Research*, Kim et al provide additional mechanistic insights into the link between obesity, innate immunity, vascular insulin resistance, and vascular inflammation in a murine model of high-fat diet-induced obesity.¹¹ The authors induced obesity in C57BL6 mice by feeding them a high-fat diet for 8 weeks. Insulin signaling in aortic tissue from high-fat-fed mice was impaired, as measured by reduced phosphorylation of AKT and eNOS in response to insulin administration consistent with cellular evidence of insulin resistance. These effects on insulin resistance were associated with evidence of activation of NF- κ B dependent inflammatory pathways, as indicated by increased phosphorylation of IKK- β and increased expression of the NF- κ B dependent proinflammatory genes IL-6 and ICAM-1.

To further characterize the signaling pathway by which high-fat diet induces insulin resistance and proinflammatory vascular response, the authors did similar studies in TLR-4-null mice. Despite comparative degrees of obesity and dyslipidemia, high-fat diet in mice lacking TLR-4 gene did not induce vascular proinflammatory gene expression or cellular evidence of insulin resistance. These observations support the contention of the authors that high-fat diet-induced obesity is associated with TLR-4-dependent vascular insulin resistance and proinflammatory signaling. These findings also extend previously reported findings of the role of innate immune signaling in insulin resistance in other tissues.⁹

The authors further demonstrate that brief in vitro exposure to palmitic acid, one of the free fatty acids that is elevated in obesity, in concentrations that are modestly higher than those observed in obesity and type II diabetes, could induce insulin resistance in aortic tissue taken from nonobese wild-type C57BL6 mice fed a normal chow but not in aortic tissue of nonobese TLR-4-null mice fed a normal chow. These observations are consistent with the hypothesis that free fatty acids mediate insulin resistance and proinflammatory vascular responses induced by high-fat diet.^{2–9,12} The authors provide additional in vitro data from a variety of elegant experiments to show that palmitate mediated insulin resistance and proinflammatory vascular signaling is dependent on activation of a cascade of intracellular pathway involving TLR-4 and its downstream adaptor molecules MyD88, IRAK, and IKK- β .

Collectively these in vivo and in vitro findings support the authors contention that high-fat diet induces vascular insulin resistance and a proinflammatory response by signaling through TLR-4/NF- κ B pathway and that such effects may be mediated, at least in part, by free fatty acids such as palmitate.¹¹ These observations extend previously reported

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

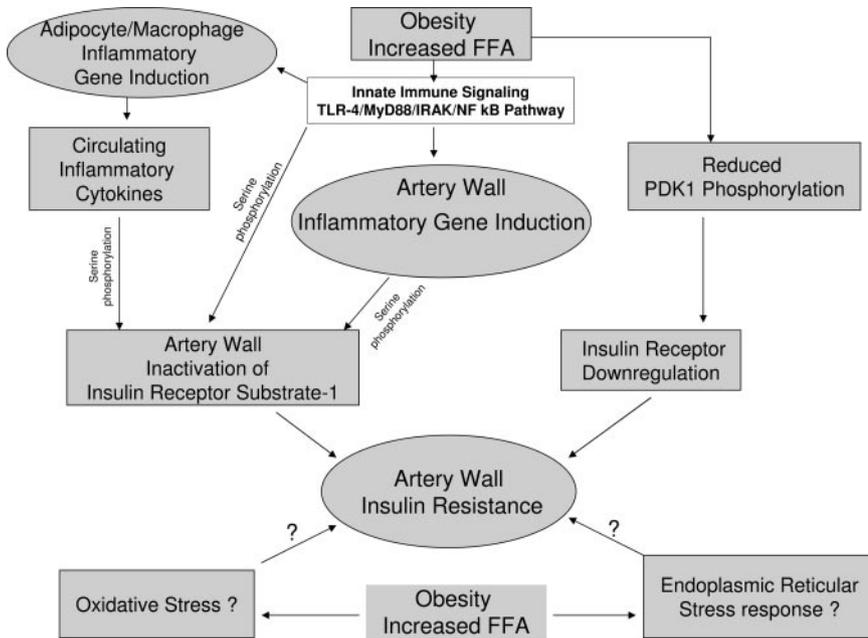
From the Division of Cardiology and Atherosclerosis Research Center, Burns and Allen Research Institute and the Department of Medicine, Cedars Sinai Medical Center and David Geffen School of Medicine at UCLA, Los Angeles, Calif.

Correspondence to P.K. Shah, MD, Director, Division of Cardiology and Atherosclerosis Research Center, Cedars Sinai Medical Center, Suite 5531, 8700 Beverly Blvd, Los Angeles, CA 90048. E-mail shahp@cshs.org

(*Circ Res.* 2007;100:1531-1533.)

© 2007 American Heart Association, Inc.

Circulation Research is available at <http://circres.ahajournals.org>
DOI: 10.1161/CIRCRESAHA.107.101104



Schematic depicts the various signaling pathways linking obesity and cellular insulin resistance and inflammation in the vasculature and extravascular tissues (see text for details). TLR indicates toll like receptor; MyD88, myeloid differentiation factor 88; FFA, free fatty acids; PDK1, PI3 dependent protein kinase 1; NF-κB, nuclear factor-κB.

work delineating the role of innate immune signaling through TLR-4/MyD88 pathway in hyperlipidemia-induced atherosclerosis in murine models and suggest that similar signaling pathways may directly contribute to accelerated vascular disease in insulin resistance syndromes.^{13–16}

Despite compelling data to support this hypothesis, certain limitations of this work should also be considered. The authors do not fully define how induction of inflammatory signaling via TLR-4 activation actually induces cellular insulin resistance. Similarly, the role of other pathways that may contribute to high-fat diet-induced insulin resistance such as increased oxidant stress, increases in TNF-α, elevated plasma glucose levels, aging, and dysregulation of the endoplasmic reticular (ER) stress response which have also been implicated in the pathogenesis of insulin resistance, have not been considered or defined.^{1,17–19} Furthermore, a potential contribution of inflammatory activation or downregulation of antiinflammatory pathways in nonvascular tissues, such as adipose tissue and macrophages, known to occur in obesity, to arterial insulin resistance and proinflammatory signaling has also not been defined.⁹ Notwithstanding these limitations, the authors have extended our knowledge regarding the potential mechanistic links between high-fat diet-induced obesity, innate immunity, impaired vascular insulin signaling, and activation of a vascular inflammatory gene program and endothelial dysfunction, events which may prime the vasculature for development of vasoocclusive disease. These observations may provide directions for novel therapeutic interventions against insulin resistance and vascular disease.

Acknowledgments

The author acknowledges the contribution of his research team.

Sources of Funding

The author is supported by the Heart Foundation, United Hostesses Charities, The Corday Foundation, and Sam Spaulding Foundation.

Disclosures

None.

References

- Steinberg GR. Inflammation in obesity is the common link between defects in fatty acid metabolism and insulin resistance. *Cell Cycle*. 2007; 6:888–894.
- Deedwania PC, Volkova N. Metabolic syndrome and cardiovascular disease: epidemiology, pathophysiology and therapeutic implications. In PK Shah, ed: *Risk Factors for Coronary Artery Disease*. London, UK: Taylor and Francis; 2006:1–34.
- Kim F, Tysseling KA, Rice J, Pham M, Haji L, Gallis BM, Baas AS, Paramsothy P, Giachelli CM, Corson MA, Raines EW. Free fatty acid impairment of nitric oxide production in endothelial cells is mediated by IKKβ. *Arterioscler Thromb Vasc Biol*. 2005;25:989–994.
- Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, Shulman GI. Mechanism of free fatty acid-induced insulin resistance in humans. *J Clin Invest*. 1996;97:2859–2865.
- Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance. *Int J Obes Relat Metab Disord*. 2003;27(Suppl 3):S49–S52.
- Hotamisligil GS. Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord*. 2003;27(Suppl 3):S53–S55.
- Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med*. 2005;11:183–190.
- Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116:1793–1801.
- Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest*. 2006;116:3015–3025.
- Dey D, Bhattacharya A, Roy S, Bhattacharya S. Fatty acid represses insulin receptor gene expression by impairing HMGA1 through protein kinase Cε. *Biochem Biophys Res Commun*. 2007;357: 474–479.
- Kim F, Pham M, Luttrell I, Bannerman DD, Tupper J, Thaler J, Hawn TR, Raines EW, Schwartz MW. Toll like receptor-4 mediates vascular inflammation and insulin resistance in diet-induced obesity. *Circ Res* 2007;100: 1589–1596.
- Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J Biol Chem*. 2001;276: 16683–16689.
- Xu XH, Shah PK, Faure E, Equils O, Thomas L, Fishbein MC, Luthringer D, Xu XP, Rajavashisth TB, Yano J, Kaul S, Ardit M. Toll-like

- receptor-4 is expressed by macrophages in murine and human lipid-rich atherosclerotic plaques and upregulated by oxidized LDL. *Circulation*. 2001;104:3103–3108.
14. Edfeldt K, Swedenborg J, Hansson GK, Yan ZQ. Expression of toll-like receptors in human atherosclerotic lesions: a possible pathway for plaque activation. *Circulation*. 2002;105:1158–1161.
 15. Bjorkbacka H, Kunjathoor VV, Moore KJ, Koehn S, Ordija CM, Lee MA, Means T, Halmen K, Luster AD, Golenbock DT, Freeman MW. Reduced atherosclerosis in MyD88-null mice links elevated serum cholesterol levels to activation of innate immunity signaling pathways. *Nat Med*. 2004;10:416–421.
 16. Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, Akira S, Rajavashisth TB, Ardit M. Lack of Toll-like receptor 4 or myeloid differentiation factor 88 reduces atherosclerosis and alters plaque phenotype in mice deficient in apolipoprotein E. *Proc Natl Acad Sci U S A*. 2004;101:10679–10684.
 17. Laine PS, Schwartz EA, Wang Y, Zhang WY, Karnik SK, Musi N, Reaven PD. Palmitic acid induces IP-10 expression in human macrophages via NF-kappaB activation. *Biochem Biophys Res Commun*. 2007;358:150–155.
 18. Suganami T, Tanimoto-Koyama K, Nishida J, Itoh M, Yuan X, Mizuarai S, Kotani H, Yamaoka S, Miyake K, Aoe S, Kamei Y, Ogawa Y. Role of the Toll-like receptor 4/NF-kappaB pathway in saturated fatty acid-induced inflammatory changes in the interaction between adipocytes and macrophages. *Arterioscler Thromb Vasc Biol*. 2007;27:84–91.
 19. Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Gorgun CZ, Hotamisligil GS. Chemical chaperones reduce ER stress and restore glucose homeostasis in mouse model of type II diabetes. *Science*. 2006;313:1137–1140.

KEY WORDS: obesity ■ insulin resistance ■ toll like receptor ■ inflammation