Immune Network
DOI 10.4110/in.2011.11.2.95
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Role of Innate Immunity in Diabetes and Metabolism: Recent Progress in the Study of Inflammasomes

*Myung-Shik Lee**
Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, Korea

Type 1 diabetes is one of the classical examples of organ-specific autoimmune diseases characterized by lymphocytic infiltration or inflammation in pancreatic islets called 'insulitis'. In contrast, type 2 diabetes has been traditionally regarded as a metabolic disorder with a pathogenesis that is totally different from that of type 1 diabetes. However, recent investigation has revealed contribution of chronic inflammation in the pathogenesis of type 2 diabetes. In addition to type 2 diabetes, the role of chronic inflammation is being appreciated in a wide variety of metabolic disorders such as obesity, metabolic syndrome, and atherosclerosis. In this review, we will cover the role of innate immunity in the pathogenesis of metabolic disorders with an emphasis on NLRP3.
[Immune Network 2011;11(2):95-99]

INTRODUCTION

Researches on inflammation have been greatly facilitated by the discovery and characterization of innate immune receptors such as TLR, NLR, RLR or CLR. Role of TLR, the first immune receptor characterized, in type 2 diabetes, obesity or atherosclerosis has been suggested in several previous papers (1,2) which can explain chronic inflammation in type 2 diabetes (3,4). In contrast, the role for NLR in metabolic disorders is being recognized only recently. Among NLRs comprising more than 20 members, NLRP family members may be particularly relevant for metabolic disorders because NLRP, as a constituent of inflammasome, plays a vital role in the maturation and release of IL-1β (5). IL-1β has been implicated in both type 1 and type 2 diabetes (6-8), and inflammasome is an essential component of the intracellular machinery for IL-1β induction and maturation in response to exogenous or endogenous stimuli ("danger signal") (9).

NLRP3 AS A SENSOR OF "DANGER SIGNAL"

Activation of NLRP has been intensely investigated. However, certain steps of NLRP activation are not clearly understood. After contact with DAMP (death-associated molecular pattern) or PAMP (pathogen-associated molecular pattern), NLRP self-oligomerizes through NACHT domain to form a high-molecular weight flatform. In the case of NLRP2 or NLRP3, they bind to an adaptor protein called ASC which has both PYD domain and CARD domain, and sometimes is also called PYCARD. Upon stimulation, PYD domain of NLRP2 or 3 associates with PYD domain of ASC through another homotypic interaction. Then, CARD domain of ASC entices CARD domain of procaspase-1. Homotypic clustering of procaspase-1 induces self-cleavage of the 'pro' domain and formation of the active caspase-1 p10/p20 tetramer, which then processes pro-IL-1β to IL-1β by cleavage of another 'pro' sequence (10) (Fig. 1). While the molecular mechanism downstream of NLRP oligomerization is well characterized, intracellular sequence leading to oligomerization of NLRP remains to be elucidated. Cytosolic delivery of PAMP through pannexin-1 hemichannel interacting with P2X7 ATP receptor, K^+ efflux, lysosomal injury and reactive oxygen species (ROS) formation have been implicated as the proximal events leading to NLRP oligomerization (10,11) (Fig. 1). Recent papers have presented evidence suggesting the role of mitochondria as a

Received on March 3, 2011. Accepted on March 7, 2011.

*Corresponding Author. Tel: 82-2-3410-3436; Fax: 82-2-3410-6491; E-mail: mslee0923@skku.edu

Keywords: Inflammasomes, NLRP, Diabetes, Metabolism

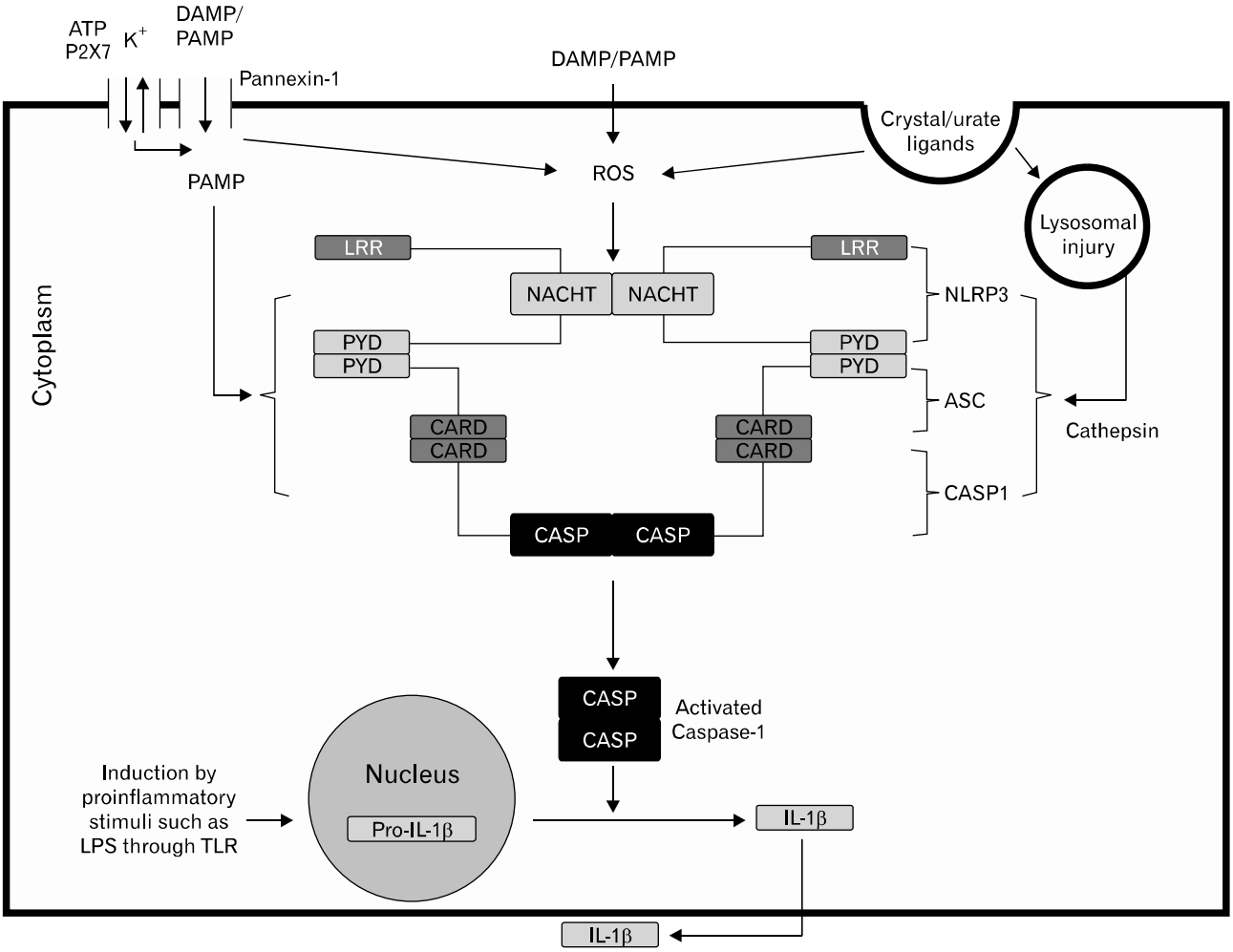

Figure 1. Pathway for NLRP3 activation. As there is no evidence of direct physical contact between ligands and NLRP3, three major pathways for NLRP3 activation have been proposed such as direct cytoplasmic delivery of bacterial ligands through pannexin-1 hemichannel, ROS production, and lysosomal injury by crystalline/particulate ligands such as cholesterol crystal or monosodium urate.

source of ROS leading to NLRP stimulation (12,13). A recent paper claimed the role of ROS in the dissociation of TXNIP from thioredoxin leading to its binding to NLRP3 and inflammasome activation (14). An interesting point in the relationship between inflammasome and metabolism is that glyburide, a well-known drug of sulfonylurea class for type 2 diabetes inhibits NLRP3 stimulation, which is independent of its effect on ATP-sensitive K_{ATP} channel (15). Effect of glyburide on sepsis has also been reported. Considering the proposed role of NLRP3 activation in type 2 diabetes and metabolic syndrome (see below), it will be an intriguing question how much of the effect of glyburide on type 2 diabetes would be explained by NLRP3 inhibition. While the role for NLRP3 is most prominent in the development of inflammation, its role in the protection of epithelial cells has also been demonstrated (16), which is reminiscent of the previously reported role of TLR in the protection of intestinal epithelial cells (17).

NLRP3 AND INSULIN RESISTANCE

Several papers have implicated diverse arms of innate immunity such as TLR, eosinophils or mast cells in insulin resistance (4,18,19). A recent paper reported the role of NLRP3 in obesity-induced inflammation and insulin resistance. In that paper, positive correlation between IL-1β (or NLRP3)

mRNA expression and body weight of calorie-restricted mice was shown. Improved glucose tolerance was also found in obese mice with targeted disruption of NLRP3. IL-1β release in response to ceramide in conjunction with LPS was also abrogated in *NLRP3*-knockout macrophages (20). However, it is still not clear if C2 ceramide used in that experiment could represent lipids associated with obesity *in vivo*. It also remains to be clarified what lipid intermediates or metabolites are able to activate inflammasome in obese subjects.

NLRL3 AND PANCREATIC ISLET CELLS

A recent paper reported the expression of NLRP3, ASC and caspase-1 in islet cells. Decreased IL-1β release from *NLRP3*-knockout islet cells was also shown. *NLRP3*-knockout mice showed improved glucose profile after high-fat diet, which was ascribed to the attenuated IL-1β release from islet cells of *NLRP3*-knockout mice (14). Hyperglycemia-induced IL-1β release was also ascribed to increased ROS in response to hyperglycemia, induction of TXNIP and subsequent activation of NLRP3. However, it is not clear whether the source of IL-1β from islet cells is β-cells or immune cells in islets such as macrophages. Altered glucose metabolism in *TXNIP*-knockout mice might be also due to causes other than NLRP3 activation (21).

A recent report showed activation of NLRP3 by islet amyloid polypeptide (IAPP). Human diabetes and murine diabetes differ from each other in several points. One of the fundamental differences between them is frequent deposition of amyloid in islets of human type 2 diabetes but not in those of murine diabetes. Such a difference is due to the difference in amino acid sequence of IAPP. Human IAPP, the major component of islet amyloid, is amyloidogenic while murine one is not, which is attributable to the difference in their amino acid sequences. Masters et al. showed that human-type IAPP is able to induce NLRP3 activation and IL-1β release from dendritic cells or macrophages primed with LPS or minimally modified LDL (mmLDL), an agonist for TLR4 (22). Such results are similar to the activation of NLRP3 of microglial cells by amyloid-β via lysosomal injury (23); however, the role of TXNIP was not evident in IAPP-induced NLRP3 activation.

NLRP3 IN OTHER TYPES OF METABOLIC DISORDERS

Atherosclerosis is also a well-known metabolic disease that has prominent inflammatory features. Role of innate immunity in the pathogenesis of atherosclerosis has been demonstrated in several *TLR*- or *MyD88*-knockout animals (3). Recent papers showed the role of NLRP3 activation by cholesterol crystals in the development of atherosclerosis (24) (Fig. 1). Lysosomal injury after phagocytosis of cholesterol crystals appears to be responsible for the activation of NLRP3. Besides cholesterol crystal, the role for mmLDL crystal in the priming of cells for NLRP3 activation was also suggested. In that case, mmLDL may be able to act as both signal 1 (priming signal) and signal for NLRP3 activation (24). Gout is also one of the classical examples related to NLRP3 activation. Gout is, in fact, one of the first metabolic diseases that involve activation of inflammasome. Crystals of monosodium urate and calcium pyrophosphate dehydrate were identified as the signals that are capable of NLRP3 activation in gout and pseudogout, respectively (25) (Fig. 1).

ROLF OF INNATE IMMUNITY IN TYPE 1 DIABETES

Type 1 diabetes is a well-known autoimmune disease that is characterized by a specific adaptive immunity against β-cell antigens. However, innate immunity plays a crucial role in the establishment of specific B- and T-cell immunity and its maintenance (26,27). We have reported that TLR, particularly TLR2, plays a critical role in the priming of naïve diabetogenic T cells in the pancreatic lymph nodes by sensing β-cell death (28) that occurs physiologically during the organogenesis of the pancreas (27). A recent study also showed possible role of innate immunity other than TLR in the development of type 1 diabetes by demonstrating the development of type 1 diabetes in *MyD88*-knockout NOD mice when they were rendered germ-free (29). However, it is not clear which types of innate immune receptors are involved in the development of autoimmunity in those *MyD88*-knockout mice. It is also not known which types of innate immunity play roles in the apparent disease inhibition by intestinal microbiota in those mice. The role for NLRP3 or NLR has not been demonstrated in the pathogenesis of type 1 diabetes. Further studies will be necessary to understand the disease-promoting or -inhibitory activity of NLR in type 1 diabetes.

CONCLUSION

Pathogenetic role of innate immunity is being generally appreciated in diabetes and metabolism that had been considered as pure metabolic disorders. TLR was the first innate immune receptors that have been studied in those diseases. Recent studies have shown important roles of non-TLR innate immune receptors, particularly NLRP3 in diverse metabolic disorders such as diabetes, atherosclerosis, obesity and gout. Further studies will be necessary to identify endogenous or exogenous ligands or activating signals for innate immune receptors involved in the pathogenesis of such diseases and to develop therapeutic agents based on the novel immunological principles.

ACKNOWLEDGEMENTS

This study was supported by the Global Research Laboratory Grant (K21004000003-10A0500-00310) and the 21C Frontier Functional Proteomics Project (FPR08B1-210) of the National Research Foundation of Korea. Lee M-S is the recipient of a grant of the Korea Healthcare Technology R&D Project (A080967) and the Bio R&D program of the Korean Ministry of Science & Technology (2008-04090).

CONFLICTS OF INTEREST

The author have no financial conflict of interest.

REFERENCES

1. Michelsen KS, Wong MH, Shah PK, Zhang W, Yano J, Doherty TM, Akira S, Rajavashisth TB, Arditi 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 101;10679-10684, 2004
2. 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 116;3015-3025, 2006
3. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D: Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15;930-939, 2009
4. Hotamisligil GS, Shargill NS, Spiegelman BM: Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259;87-91, 1993
5. Kufer TA, Sansonetti PJ: NLR functions beyond pathogen recognition. Nat Immunol 12;121-128, 2011
6. Kim S, Kim HS, Chung KW, Oh SH, Yun JW, Im SH, Lee MK, Kim KW, Lee MS: Essential role for signal transducer and activator of transcription-1 in pancreatic beta-cell death and autoimmune type 1 diabetes of nonobese diabetic mice. Diabetes 56;2561-2568, 2007
7. Kim S, Millet I, Kim HS, Kim JY, Han MS, Lee MK, Kim KW, Sherwin RS, Karin M, Lee MS: NF-kappa B prevents beta cell death and autoimmune diabetes in NOD mice. Proc Natl Acad Sci U S A 104;1913-1918, 2007
8. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY: Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 356;1517-1526, 2007
9. Gallucci S, Lolkema M, Matzinger P: Natural adjuvants: endogenous activators of dendritic cells. Nat Med 5;1249-1255, 1999
10. Schroder K, Tschopp J: The inflammasomes. Cell 140;821-832, 2010
11. Kanneganti TD, Lamkanfi M, Kim YG, Chen G, Park JH, Franchi L, Vandenabeele P, Núñez G: Pannexin-1-mediated recognition of bacterial molecules activates the cryopyrin inflammasome independent of Toll-like receptor signaling. Immunity 26;433-443, 2007
12. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, Englert JA, Rabinovitch M, Cernadas M, Kim HP, Fitzgerald KA, Ryter SW, Choi AM: Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 12;222-230, 2011
13. Zhou R, Yazdi AS, Menu P, Tschopp J: A role for mitochondria in NLRP3 inflammasome activation. Nature 469;221-225, 2011
14. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J: Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol 11;136-140, 2010
15. Lamkanfi M, Mueller JL, Vitari AC, Misaghi S, Fedorova A, Deshayes K, Lee WP, Hoffman HM, Dixit VM: Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. J Cell Biol 187;61-70, 2009
16. Zaki MH, Boyd KL, Vogel P, Kastan MB, Lamkanfi M, Kanneganti TD: The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis. Immunity 32;379-391, 2010
17. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R: Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 118;229-241, 2004
18. Liu J, Divoux A, Sun J, Zhang J, Clément K, Glickman JN, Sukhova GK, Wolters PJ, Du J, Gorgun CZ, Doria A, Libby P, Blumberg RS, Kahn BB, Hotamisligil GS, Shi GP: Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. Nat Med 15;940-945, 2009
19. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, Chawla A, Locksley RM: Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. Science 332;243-247, 2011

20. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD: The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 17;179-188, 2011
21. Oka S, Yoshihara E, Bizen-Abe A, Liu W, Watanabe M, Yodoi J, Masutani H: Thioredoxin binding protein-2/thioredoxin-interacting protein is a critical regulator of insulin secretion and peroxisome proliferator-activated receptor function. Endocrinology 150;1225-1234, 2009
22. Masters SL, Dunne A, Subramanian SL, Hull RL, Tannahill GM, Sharp FA, Becker C, Franchi L, Yoshihara E, Chen Z, Mullooly N, Mielke LA, Harris J, Coll RC, Mills KH, Mok KH, Newsholme P, Nuñez G, Yodoi J, Kahn SE, Lavelle EC, O'Neill LA: Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1β in type 2 diabetes. Nat Immunol 11;897-904, 2010
23. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ, Golenbock DT: The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol 9;857-865, 2008
24. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nuñez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E: NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 464;1357-1361, 2010
25. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J: Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 440;237-241, 2006
26. Jun HS, Santamaria P, Lim HW, Zhang ML, Yoon JW: Absolute requirement of macrophages for the development and activation of beta-cell cytotoxic CD8+ T-cells in T-cell receptor transgenic NOD mice. Diabetes 48;34-42, 1999
27. Turley S, Poirot L, Hattori M, Benoist C, Mathis D: Physiological beta cell death triggers priming of self-reactive T cells by dendritic cells in a type-1 diabetes model. J Exp Med 198;1527-1537, 2003
28. Kim HS, Han MS, Chung KW, Kim S, Kim E, Kim MJ, Jang E, Lee HA, Youn J, Akira S, Lee MS: Toll-like receptor 2 senses beta-cell death and contributes to the initiation of autoimmune diabetes. Immunity 27;321-333, 2007
29. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, Hu C, Wong FS, Szot GL, Bluestone JA, Gordon JI, Chervonsky AV: Innate immunity and intestinal microbiota in the development of Type 1 diabetes. Nature 455;1109-1113, 2008