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Editorial

NLRP3 Inflammasome and Obesity: A Framework of Situation

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Obesity puts people at risk for a variety of IL-1-driven metabolic disorders, such as atherosclerosis and type 2 diabetes mellitus (T2D) [1]. Moreover, the activation of adipose tissue macrophages (ATMs) inside fat deposits has been associated to an obesity-induced inflammatory state [2]. Furthermore, a new study found that obesity promotes the NLRP3 inflammasome to assemble in ATMs, resulting in insulin resistance in early T2D patients [3]. Higher level of both NLRP3 and IL-1 in visceral adipose tissue in free-feeding mice on a conventional chow diet was observed to associate significantly with body weight and adiposity when matched to mice fed a calorie-restricted diet. Weight loss in obese T2D patients was linked to lower NLRP3 and IL-1β expression in subcutaneous adipose tissue, which was similar to the findings in mice. Gene-deficient mice fed a high fat diet demonstrated lower caspase-1 activation and pro-IL-1β expression in adipose tissue, as well as a loss in serum IL-18 synthesis, compared to their wildtype counterparts. Furthermore, NLRP3- and caspase-1-deficient animals are more resistant to insulin resistance caused by a high-fat diet [3,4]. Insulin sensitivity was observed to be reduced as a result of NLRP3 inflammasome-mediated activation of effector adipose T cells, which then mediate downstream insulin resistance pathways via releasing interferon-gamma [5].

A plethora of sterile danger signals created in adipose tissues could activate tissue-resident immune cells including macrophages and dendritic cells, leading to the creation of an NLRP3 inflammasome. Ceramide, a lipid molecule made up of sphingoside and fatty acid, could be one natural danger signal that causes NLRP3 activation in obese people [6]. Circulating amounts of free fatty acids rise during obesity, which are likely to be scavenged by ATMs and converted to ceramide [7]. NLRP3-dependent caspase-1 activation and IL-1β production were observed in LPS-primed macrophages activated with ceramide, albeit at modest levels [3]. Adipose tissue explants from diet-induced obese mice showed increased caspase-1 cleavage in response to ceramide. Alternative endogenous triggers, such as material produced by dying cells or crystalline chemicals, could activate NLRP3 in this disease scenario, albeit no proof has been reported. Saturated fatty acid palmitate, another lipid, has recently been identified to activate the NLRP3 inflammasome [8]. Palmitate is one of the most common free fatty acids in plasma, and it is found in substantially higher concentrations in obese people. Although the unsaturated fatty acid oleate is prevalent in plasma, it has not been shown to activate the NLRP3 inflammasome like palmitate [9]. Palmitate appears to activate NLRP3 by a new mechanism involving diminished AMP-protein kinase (AMPK) activity, which leads to a defective autophagic process and the buildup of mitochondrial ROS, in contrast to other known NLRP3 activators. This matches previous study that suggested mitochondrial ROS may be essential for NLRP3 activation [10,11]. According to the findings, activation of NLRP3 by palmitate and subsequent IL-1 production enhances insulin resistance both directly, through suppression of insulin signaling, and indirectly, through increased production of TNF, a known inducer of insulin resistance [12,13].

Obesity rates are rising at the same time as the prevalence of various inflammatory-driven metabolic diseases, such as atherosclerosis and T2D [14]. NLRP3 is a common receptor that is activated in response to a number of metabolic risk factors, according to the studies mentioned above. In a variety of metabolic diseases, obesity can also supply the priming signals required for NLRP3 activation, removing

the safety switch from NLRP3 signaling. This could explain why persons who are overweight are more prone to NLRP3-dependent viral and environmental infections, as well as metabolic illnesses like atherosclerosis, T2D, and gout [15].

Endogenous chemicals known to activate the NLRP3 inflammasome have been observed to increase and accumulate at local tissue locations during obesity. In both atherosclerosis and T2D, modified LDL is one such chemical that is likely to prepare macrophages *in vivo* for later NLRP3 activation. Free fatty acid circulation is also enhanced in obesity and can build up in adipose tissues as T2D progresses [16]. Free fatty acids, like modified LDL, can trigger NF-B signaling via TLR4 [17], and so potentially serve as an alternate priming signal for the NLRP3 inflammasome in T2D. Obesity increases TLR2 and TLR4 expression in adipose tissue [18], and TLR4 deficiency in mice has been demonstrated to protect against fat-induced inflammation and insulin resistance [19,20]. Many additional unidentified NLRP3 priming chemicals are likely to exist in obesity, and their discovery will bring new insights into metabolic disorders. In conclusion, obesity-related inflammation can prepare cells to activate the NLRP3 inflammasome, making it a prospective therapeutic target.

Disclosure Statement

The author declares that there are no conflicts of interest.

Bibliography

1. Ellulu MS., *et al*. "Obesity and inflammation: the linking mechanism and the complications". *Archives of Medical Science* 13.4 (2017): 851-863.

2. Van Dierendonck XAMH., *et al*. "The role of uncoupling protein 2 in macrophages and its impact on obesity-induced adipose tissue inflammation and insulin resistance". *Journal of Biological Chemistry* 295.51 (2020): 17535-17548.

3. Vandanmagsar B., *et al*. "The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance". *Nature Medicine* 17.2 (2011): 179-188.

4. Li Y., *et al*. "Inflammasomes as therapeutic targets in human diseases". *Signal Transduction and Targeted Therapy* 6.1 (2021): 247.

5. Gora IM., *et al*. "NLRP3 Inflammasome at the Interface of Inflammation, Endothelial Dysfunction, and Type 2 Diabetes". *Cells* 10.2 (2021): 314.

6. Reginato A., *et al*. "The Role of Fatty Acids in Ceramide Pathways and Their Influence on Hypothalamic Regulation of Energy Balance: A Systematic Review". *International Journal of Molecular Science*s 22.10 (2021): 5357.

7. Russo L and Lumeng CN. "Properties and functions of adipose tissue macrophages in obesity". *Immunology* 155.4 (2018): 407-417.

8. Karasawa T and Takahashi M. "Saturated fatty acid-crystals activate NLRP3 inflammasome". *Aging* 11.6 (2019): 1613-1614.

9. Tzeng HT., *et al*. "Shaping of Innate Immune Response by Fatty Acid Metabolite Palmitate". *Cells* 8.12 (2019): 1633.

10. Guo X., *et al*. "AKT controls NLRP3 inflammasome activation by inducing DDX3X phosphorylation". *FEBS Letters* (2021).

11. Li D., *et al*. "Reactive oxygen species induced by uric acid promote NRK 52E cell apoptosis through the NEK7 NLRP3 signaling pathway". *Molecular Medicine Reports* 24.4 (2021): 729.

12. Snodgrass RG., *et al*. "Inflammasome-mediated secretion of IL-1β in human monocytes through TLR2 activation; modulation by dietary fatty acids". *Journal of Immunology* 191.8 (2013): 4337-4347.

13. Sokolova M., *et al*. "Palmitate promotes inflammatory responses and cellular senescence in cardiac fibroblasts". *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1862.2 (2017): 234-245.

14. Finelli C. "Obesity, COVID-19 and immunotherapy: the complex relationship!". *Immunotherapy* 12.15 (2020): 1105-1109.

15. Fusco R., *et al*. "Focus on the Role of NLRP3 Inflammasome in Diseases". *International Journal of Molecular Sciences* 21.12 (2020): 4223.

16. Kelley N., *et al*. "The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation". *International Journal of Molecular Sciences* 20.12 (2019): 3328.

17. Rocha DM., *et al*. "Saturated fatty acids trigger TLR4-mediated inflammatory response". *Atherosclerosis* 244 (2016): 211-215.

18. Rogero MM and Calder PC. "Obesity, Inflammation, Toll-Like Receptor 4 and Fatty Acids". *Nutrients* 10.4 (2018): 432.

19. He W., *et al*. "Ageing potentiates diet-induced glucose intolerance, β-cell failure and tissue inflammation through TLR4". *Scientific Reports* 8.1 (2018): 2767.

20. Hasan A., *et al*. "TNF-α in Combination with Palmitate Enhances IL-8 Production via The MyD88- Independent TLR4 Signaling Pathway: Potential Relevance to Metabolic Inflammation". *International Journal of Molecular Sciences* 20.17 (2019): 4112.

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