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Editorial

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NLRP3 Inflammasome Signaling Platform as New Pharmacological Target for Metaflammation

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Metaflammation is a metabolic inflammatory state characterized by chronic, low-grade inflammatory response initiated by excess nutrients in metabolic cells.[1] The inflammatory signaling conducted by the metabolic cell eventually causes activation of specialized immune cells and leads to an unresolved inflammatory response within the tissue.[2] The high level of co-ordination of inflammatory and metabolic pathways is highlighted by the overlapping biology and function of macrophages and adipocytes in obesity. Preadipocytes under some conditions can exhibit phagocytic and antimicrobial properties and appear to even be able to differentiate into macrophages in the right environment, which suggests a potential immune role for preadipocytes. Furthermore, macrophages and adipocytes co-localize in white adipose tissue in obesity. Macrophages in adipose tissue are likely to contribute to the production of inflammatory mediators either alone or in concert with adipocytes, which suggests a potentially important influence of macrophages in promoting insulin resistance. Besides macrophages, obesity is associated with aberrant expansion of other leukocytes (T-cells, B-cells, eosinophils, neutrophils and mast cells) in adipose tissue that contribute to chronic inflammation. In particular, the increased neutrophils lead to a rise of myeloperoxidase (MPO) activity, a marker of neutrophil infiltration, in the damaged tissue during inflammation.[3] Despite the role of meta-inflammation, in promoting metabolic diseases, including obesity and insulin resistance, is well known,[4] from a therapeutic perspective, only limited experience is available regarding the inhibition of specific inflammatory pathways activated by the metabolic, biochemical and haemodynamic derangements known to exist in CMD. Thus, effective treatments that halt or induce regression of meta-inflammation have potential to provide an immense clinical, social and economic benefit. Most recent evidences suggest a substantial role of the NLRP3 inflammasome in regulating meta-inflammation. The term "inflammasome" was coined by Tschopp and co-workers in 2002 to describe a high-molecular-weight complex present in the cytosol of stimulated immune cells that mediates the activation of inflammatory caspases.[5] To date, five receptor proteins have been confirmed to assemble inflammasomes, including the nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein (NLR) family members NLRP1, NLRP3 and NLRC4, as well as the proteins absent in melanoma 2 (AIM2) and pyrin. The best-characterized inflammasome is the NLRP3 inflammasome which interacts with an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), thus recruiting and activating caspase-1. Because caspase-1 is an IL-1β-converting enzyme, it mediates the processing of pro-IL-1β into mature IL-1β and the consequent release of IL-1β, thereby causing inflammation. Yet, the induction of IL-1β release requires the transcriptional induction of pro-IL-1β. Thus, a system including pro-IL-1β induction and inflammasome-mediated IL-1β maturation seems necessary for the regulation of this inflammatory cytokine. The assembly of functional NLRP3 inflammasome requires two distinct steps, priming and activation, respectively at the transcriptional and post-transcriptional levels. Furthermore, it is necessary to prime for a long time to increase the cellular expression of NLRP3 through NF-κB signaling. Post-transcriptional molecular mechanisms controlling NLRP3 activation that can respond quickly to stimuli without the need for NF-κB activation and new protein synthesis have also been identified. Extracellular signal-regulated kinase 1 (ERK1)-mediated post-translational modifications also permit the NLRP3 inflammasome to respond to the second signal, ATP, by inducing post-translational events that are independent of any new production of pro-IL-1β or

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NLRP3 protein.

Impaired inflammasome activity has been incriminated in the pathogenesis of obesity and insulin resistance.[6-10] We recently reported that the chronic exposure of rats to the most widely used added sugar high-fructose corn syrup (HFCS-55), used as ingredients in processed or prepared foods and caloric beverages, evokes metabolic abnormalities and renal dysfunction/inflammation, which are associated with significant increase local expression and activity of the NLRP3 inflammasome complex.[11] We also contributed to demonstrate that increased expression of inflammasome-related components is associated with the development of hepatic steatosis.[12,13] Interestingly, recent evidence convincingly show that NLRP3 inflammasome activation is sustained not only by liver innate immunity cells but also by parenchymal cells,[14-16] with studies indicating that saturated fatty acids can specifically induce NLRP3 inflammasome-dependent IL-1β release in hepatocytes.[14,16] Many reagents that target the inflammasome products IL-1β and IL-18, including the recombinant IL-1Ra anakinra, the neutralizing IL-1β antibody canakinumab, the soluble decoy IL-1 receptor rilonacept, IL-18–binding protein, soluble IL-18 receptors and anti–IL-18 receptor monoclonal antibodies, have been developed to treat autoinflammatory diseases.[17] However, only the evaluation of small molecules that are able to selectively inhibit the NLRP3 inflammasome may allow a better understanding of the role of the NLRP3 inflammasome-caspase-1-IL-1β/18 axis in the development of selected diseases and the future design of novel and effective therapeutics. Unfortunately, so far, efficacious NLRP3 inflammasome inhibitors are still at an early stage of development. Notably, selective inhibition of NLRP3 by small molecules might present certain advantages over the use of biological agents targeted at IL-1β and its receptor, including fewer immunosuppressive effects and better pharmacokinetics and cost-effectiveness. Interestingly, we reported the effects of the selective inhibitor BAY 11-7082 on the metabolic alterations caused by chronic exposure to refined fat and fructose, the main ingredients of most processed foods, in mice. Our results demonstrated that the defects in the insulin signaling observed in both the livers and skeletal muscles of mice exposed to the hypercaloric diet could be restored by pharmacological inhibition of NLRP3 activity.[12] More recently, we demonstrated that animals exposed to the hypercaloric diet and treated with empagliflozin, a member of the novel class of antidiabetic drugs inhibitors of the sodium glucose cotransporter (SGLT)-2, showed a dose-dependent decrease of NLRP3 activation in the kidney.[18] This effect was associated with improvement in renal function, thus further confirming previous evidence showing that renal NLRP3 inflammasome inhibition may counteract development of diabetic nephropathy and chronic kidney disease.[19-21]

Overall, most recent evidence from the literature support the view that metaflammation and specifically activation of the NLRP3 inflammasome drive the development of metablic disorders and the associated end-organ injury. Most notably, they reveal new scientific horizons in the identification of strategies for the development of novel and promising treatment options for metabolic disease based on the counteracting of the low grade chronic inflammation.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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