Targeting the NLRP3 inflammasome to reduce diet-induced metabolic abnormalities in mice

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Although the molecular links underlying the causative relationship between chronic low-grade inflammation and insulin resistance are not completely understood, compelling evidence suggests a pivotal role of the NLRP3 inflammasome, a large multimeric danger-sensing platform that promotes autocatalytic activation of the cysteine protease caspase-1 and mediates the cleavage of inactive pro-IL-1β and IL-18 into their active forms [1]. We and others have recently demonstrated that either a high fat diet or a high sugar diet evoke NLRP3 inflammasome formation and activation in target organs of metabolic inflammation [2, 3].

Here we tested the hypothesis that either a selective pharmacological inhibition or a genetic ablation of the NLRP3 inflammasome results in reduction of the diet-induced metabolic alterations.

Male C57/BL6 wild-type mice and NLRP3$^{-/-}$ littermates were fed control diet or high-fat high-fructose diet (HD). A sub-group of HD-fed wild-type mice was treated with the NLRP3 inflammasome inhibitor BAY 11-7082 (3 mg/kg, i.p.).

HD-feeding increased plasma and hepatic lipids and impaired glucose homeostasis and renal function. None of these metabolic abnormalities were detected in HD-fed NLRP3$^{-/-}$ mice and they were dramatically reduced by BAY 11-7082. The improved glucose tolerance by NLRP3 pharmacological and genetic inhibition was at least partially mediated by enhancing the insulin-related signaling pathway in the liver of HD-fed mice. Treatment of WT mice with BAY 11-7082 attenuated also the renal injury (histology) and dysfunction (albuminuria) caused by HD to a degree that was very similar to that seen in mice in which the NLRP3 inflammasome had been deleted. BAY 11-7082 attenuated the diet-induced increase in NLRP3 inflammasome expression, resulting in inhibition of hepatic and renal caspase-1 activation and interleukin-(IL)-1β and IL-18 production. Interestingly, BAY 11-7082, but not gene silencing, inhibited NF-kB nuclear translocation in the same organs.

We demonstrate here for the first time that the selective pharmacological inhibition of the NLRP3 inflammasome attenuates the metabolic abnormalities and the related organ damage caused by chronic exposure to HD, with effects similar to those obtained by NLRP3 gene silencing. Interestingly, the use of the selective inflammasome inhibitor BAY11-7082, which was administered only for the last 7 weeks of the 12 weeks-dietary manipulation, demonstrates that the deleterious effects of HD exposure may be reverted by the pharmacological modulation of the NLRP3 inflammasome. Together these findings provide compelling evidence that the NLRP3 inflammasome may represent an innovative pharmacological target for insulin resistance and target organ dysfunction. The use of small molecules as selective inhibitors of NLRP3 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. Further preclinical and clinical studies are needed to further explore this possibility and to investigate/ensure the safety of this innovative pharmacological approach.

References

1. Benetti E, Chiazza F, Patel NS, Collino M. Mediators Inflamm. 2013;2013:678627.
2. Collino M, Benetti E, Rogazzo M, Mastrocola R, Yaqoob MM, Aragno M, Thiemermann C, Fantozzi R. Biochem Pharmacol. 2013;85(2):257-64.
3. Paternostro C.; E. Benetti; S. Cannito; E. Novo; F. Chiazza; M. Rogazzo; C. Bocca; R. Fantozzi; D. Povero; A. Feldstein; M. Collino; M. Parola. Journal of Hepatology 2014 vol. 60: S153