Dipeptidyl Peptidase-4 Inhibitor Linagliptin Attenuates Endotoxemia-Activated Inflammasome in Visceral Adipose Tissue of Mice Fed a High Fat Diet

Elena Dozio[1,2], Francesca Bianchi[1,3], Francesco Bandera[1,4], Elena Vianello[1,2], Lorenza Tacchini[1,2], Massimiliano M. Corsi Romanelli[1,5]

[1]Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy
[2]Laboratorio Sperimentale Ricerche Biomarcatori di Danno d'Organo, Istituto Auxologico, IRCCS, Milan, Italy
[3]Laboratorio di Morfologia Umana Applicata, IRCCS Policlinico San Donato, Milan, Italy
[4]Unità di Scompenso Cardiaco e Riabilitazione Cardiologica, IRCCS MultiMedica, Sesto San Giovanni, Milan, Italy
[4]Dipartimento di Patologia Clinica e Sperimentale Istituto Auxologico, IRCCS, Milan, Italy

Introduction: Inflammasomes are multimeric protein complexes that assembly in the cell cytoplasm in response to different stressors and activate pro-inflammatory responses. Inflammasomes can promote different diseases, including adipose tissue dysfunction and obesity-related complications. The dipeptidyl peptidase-4 (DPP-4) inhibitor Linaglipitin (L), used for type 2 diabetes mellitus, was shown to reduce obesity-related inflammation regardless its hypoglycemic effects. By using a mouse model of diet induce-obesity, we explored the effect of L on high fat diet (HF)-induced inflammasomes in visceral adipose tissue (VAT). The final aim was to highlight off target effect of L.

Materials and Methods: Twenty-four 6-week-old male C57BL/6N mice (Charles River Laboratories, Calco, Italy) were divided into 3 groups and fed for 15 weeks as follows: 1) normal chow diet (NC) with 10% calories from fat, 2) HF with 60% calories from fat and 3) HF with Linagliptin (HFL, 120 µg/die) (Boehringer Ingelheim, Milan, Italy). VAT and serum samples were collected and stored at -80° until analyses (Authorization n. 467/2022-PR). The RT² Profiler PCR Arrays allowed the detection of 84 key gene transcripts related to mouse inflammasomes (PAMM-097ZF, QIAGEN, Milan, Italy). Lipopolysaccharide binding protein (LBP) was quantified by the Mouse LBP SimpleStep ELISA® Kit by Abcam (Cambridge, UK). Serum chemokines and cytokines were quantified by the Mouse Magnetic Luminex Discovery Assay kit (R&D System, Minneapolis, MN) and the Bio-Rad Bio-Plex (Bio-Rad Laboratories, Milan, Italy).

Results: In VAT, 17 gene transcripts were upregulated and 2 down regulated by HF. Of interest, the up regulation of different components of the NLRC4 inflammasome (NLR Family CARD domain containing 4), a critical component of defense against enteric pathogen, and caspase-1 were reduced by L (fold decrease > 2). HF increased LBP level ($p < 0.001$ vs. NC). L reduce it of about 30% ($p < 0.01$ vs. HF). L also significantly blocked the increase of chemokine (C-C motif) ligand-11 (CCL11) induced by HF ($p < 0.01$). Levels of chemokine (C-C motif) ligand-7 (CCL7) and interleukin-17A (IL-17A) were lower in HFL than NC group ($p<0.05$), but unaffected by HF. Chemokine (C-C motif) ligand-5 (CCL5), interleukin-10 (IL-10), interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) were below the test sensitivity.

Conclusions: HF-diet induced obesity is characterized by endotoxemia, as suggested by the increased level of LBP in serum. Up-regulation of NLRC4 inflammasome in VAT could be the link between endotoxemia and VAT inflammation. L protected against endotoxemia, maybe both working on gut permeability and VAT responses, and modulated chemotactic signals for immune cells that can be involved in VAT inflammation and adipocyte browning.

Acknowledgements: PSR2022_Università degli Studi di Milano, RICERCA CORRENTE 2023_ Istituto Auxologico.