P1939

Tumor necrosis factor receptor-associated factor 5 (TRAF-5) deficiency exacerbates diet-induced adipose tissue inflammation and aggravates metabolic syndrome in mice

M.C. Gissler[1], N. Anto Michel[1], J. Pennig[1], P. Scherrer[1], K. Pfeiffer[1], C. Haerdtner[1], D. Von Elverfeldt[2], N. Hoppe[1], P. Stachon[1], N. Machulsky[1], I. Hilgendorf[1], C. Bode[1], D. Wolf[1], A. Zirlik[3], F. Willecke[1]

[1]University of Freiburg, Faculty of Medicine, Heart Center Freiburg University, Department of Cardiology and Angiology I, Freiburg, Germany; [2]University of Freiburg, Department of Radiology, Medical Physics, Freiburg, Germany; [3]Medical University of Graz, Department of Cardiology, Graz, Austria

Funding Acknowledgement: Forschungskommission Medizinische Fakultät Universität Freiburg, MOTI-VATE Promotionskolleg der Medizinischen Fakultät Freiburg (EKFS)

Introduction: Many clinical and experimental observations have established an association between visceral obesity and chronic adipose tissue inflammation. Potent pro-inflammatory mediators such as TNFα, CD40 and IL-1β are regulated by Tumor necrosis factor (TNF) receptor-associated factors (TRAFs). TRAF5 deficiency accelerates atherogenesis in mice by increasing inflammatory leukocyte recruitment. Since inflammatory cell invasion is also a prerequisite of adipose tissue inflammation, we tested the hypothesis that deficient TRAF5 signaling aggravates adipose tissue inflammation and its metabolic complications in a murine diet-induced obesity (DIO) model.

Purpose: We aimed to clarify the role of TRAF5 in adipose tissue inflammation and metabolic syndrome.

Methods: TRAF5–/– mice and gender- and age-matched wild-type (WT) mice consumed a high fat diet (HFD, 45%kcal from fat) or a matched low-fat diet (LFD, 10%kcal from fat) for 18 weeks to induce DIO and adipose tissue inflammation. All mice were then subjected to subsequent analysis, including glucose and insulin tolerance testing, body composition assessment by MRI imaging, flow cytometry, gene expression of different tissues, plasma analysis and histology. Finally, we studied if TRAF5 expression was associated with metabolic syndrome in humans by analyzing plasma and adipocytes samples from 62 patients of the Tumor-Necrosis-Factor Receptor Associated in Cardiovascular Risk Study (TRAFICS).

Results: TRAF5 expression was significantly attenuated in isolated WT-adipocytes and WT-macrophages after 18 weeks of HFD compared to LFD-fed controls. TRAF5–/– mice on HFD gained significantly more weight compared to TRAF5-competent mice and showed an aggravated metabolic phenotype, including impaired insulin tolerance, hyperinsulinemia and increased fasting glucose plasma levels. The weight gain in TRAF5–/– mice was attributable to a significant increase in adipose tissue and liver weight. Further analysis of the visceral adipose tissue revealed enhanced macrophage accumulation and increased pro-inflammatory CD11c+ subset polarization in HFD-fed TRAF5–/– mice. In line with an increased migratory capacity of inflammatory cells, we observed enhanced peritoneal invasion of leukocytes and subsets in TRAF5–/– mice. Accordingly, TRAF5 deficiency increased inflammatory cytokine expression and ameliorated parameters of insulin sensitivity in adipose tissue. Finally, patients with metabolic syndrome displayed decreased TRAF5 expression in blood and adipocytes compared to humans without metabolic syndrome.

Conclusion: We show that genetic deficiency of TRAF5 aggravates metabolic syndrome in murine diet-induced obesity. Enhanced accumulation of leukocytes subsets in adipose tissue serves as the likely mechanism. We conclude that TRAF5 signaling properties may favorably affect metabolic disease.