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Organizers: Miodrag L. Lukic, Janko Nikolich-Zugich, Stipan Jonjic

UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES

Immunometabolic Differences in Prototypical Th1- And Th2-Type Mouse Strains in High-Fat Diet Induced Obesity

Nemanja Jovicic[1,2], Nada Pejnovic[1,3], Ilija Jeftic[1,3], Ivan Jovanovic[1], Gordana Radosavljevic[1], Nebojsa Arsenijevic[1], Miodrag L. Lukic[1]

[1]Center for Molecular Medicine and Stem Cell Research
[2]Institute of Histology
[3]Institute of Pathophysiology, Faculty of Medical Sciences, University of Kragujevac, Serbia

Introduction & Aims: The inherent susceptibility to obesity-related metabolic disorders and type of immune/inflammatory response in metabolic tissues in mouse strains are markedly dependent on the genetic background which may affect the translation of experimental data to human pathology. Therefore, we have investigated the strain-dependent differences of visceral adipose tissue (VAT) and liver immunophenotype, liver steatosis, inflammation and fibrosis in experimental model of high-fat diet induced obesity in C57BL/6 and BALB/c, the prototypical Th1 and Th2 mouse strains.

Methods: Male 8-week old C57BL/6 and BALB/c mice were placed on HFD (60% kcal fat) or standard chow diet (10% kcal fat) for 24 weeks. We performed histological and liver and adipose tissue immunophenotypic analyses as well as expression of hepatic profibrogenic and lipid metabolism-related genes.

Results: After 24 weeks of dieting BALB/c mice exhibited higher weight gain on standard diet, while C57Bl/6 mice exhibited higher weight gain on HFD. In comparison to BALB/c mice, the amount of visceral fat and fasting blood glucose levels was higher in C57Bl/6 mice on both, chow and HFD. In contrast to BALB/c mice, HFD induced a significant increase of the amount of VAT and number of VAT associated $CD3^+CXCR3^+$ Th1 cells, dendritic cells (DCs) and $F4/80^+$ macrophages in C57Bl/6 mice. In livers, more numerous $CD3^+$ and $CD8^+$ T lymphocytes, myeloid DCs, proinflammatory macrophages ($F4/80^+CD11b^+CD11^+$ and$F4/80^+IL\text{-}1\beta^+$) and $CD11b^+Ly6C^{+high}$ monocytes and higher levels of IL-6, TNF-α and IFN-γ were detected in HFD-fed C57Bl/6 mice than in diet-matched BALB/c mice. HFD-fed C57Bl/6 mice had scarce liver steatosis in contrast to BALB/c mice which had marked hepatic steatosis and increased expression of genes related to lipid metabolism with higher serum levels of cholesterol and triglycerides and lower glycogen deposition in the liver. HFD induced prominent liver fibrosis in C57Bl/6 mice while BALB/c mice developed scarce liver collagen deposition. The expression of mRNA for procollagen, profibrogenic IL-13 and TGF-β in liver and the levels of IL-33, IL-13 and TGF-β in sera and liver homogenates were higher in HFD-fed C57Bl/6 mice compared to diet-matched BALB/c mice.

Conclusion: The obtained results indicate that Th1-type mice are susceptible to obesity, liver inflammation and fibrosis while Th2-type mice to liver steatosis in response to obesogenic HFD which is associated with differential phenotypes of immune cells in metabolic tissues. Immunometabolic differences in relation to Th1 and Th2 dominance may be relevant for studies of obesity-associated metabolic diseases in humans.