European Federation of
Immunological Societies

3rd BELGRADE EFIS SYMPOSIUM ON IMMUNOREGULATION
Immunity, Infection, Autoimmunity and Aging

Hotel Izvor, Arandjelovac Spa (Belgrade)

24-27 May 2015

IMMUNOLOGICAL SOCIETY OF SERBIA

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

UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES

Galectin-3 Promotes Hepatic Inflammation and Fibrosis in Obesogenic Mouse Model of Nonalcoholic Steatohepatitis

Ilija Jeftic[1,3] ,Nemanja Jovicic[1,2], Jelena Pantic[1], Nebojsa Arsenijevic[1], Miodrag L. Lukic[1], Nada Pejnovic[1,3]

[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: Galectin-3 (Gal-3), a β-galactoside-binding lectin, is involved in the regulation of obesity, metaflammation, and type 2 diabetes, but its role in the pathogenesis of obesity-associated non-alcoholic steatohepatitis (NASH) is incompletely defined. In this study, we aimed to dissect the role of Gal-3 in liver inflammatory response and fibrosis, key parameters in the pathogenesis and progression of NASH, induced by obesogenic high-fat diet (HFD).

Methods: Gal-3-deficient (LGALS3$^{-/-}$) and wild-type (LGALS3$^{+/+}$) C57Bl/6 mice received HFD (60% kcal fat) or standard chow diet (10% kcal fat) for 24 weeks and metabolic parameters, gene expression and immunophenotypic analyses were performed.

Results: In comparison to WT mice, HFD-fed LGALS3$^{-/-}$ mice developed increased obesity, type 2 diabetes and more pronounced liver steatosis which was accompanied by upregulation of hepatic FAS, PPAR-γ and Cd36 expression. However, ALT and AST levels, liver injury, inflammation and fibrosis scores, and hepatic procollagen and α-SMA mRNA expression were significantly increased in HFD-fed WT mice compared to diet-matched LGALS3$^{-/-}$ mice. The more pronounced hepatic fibro-inflammatory response induced by obesogenic diet in WT mice was associated with increased myeloid DCs and proinflammatory monocytes/macrophages infiltrated into the livers, and higher hepatic CCL2, NLRP3 inflammasome and IL-1β mRNA expression. Furthermore, the levels of profibrogenic IL-33 and IL-13 in liver homogenates and IL-33, ST2 and IL-13 mRNA expression in liver were markedly higher in WT than in LGALS3$^{-/-}$ mice on HFD, while hepatic expression of TGF-β were similar. Moreover, in contrast to WT macrophages, *in vitro* stimulated LGALS3$^{-/-}$ peritoneal macrophages with recombinant mouse IL-33 failed to upregulate ST2 expression and IL-13 production.

Conclusion: Gal-3 attenuates steatosis, but promotes liver injury, inflammation and fibrosis, thus participates in the progression of NASH induced by obesogenic diet in mice. Further, we show for the first time that Gal-3 plays an important regulatory role in the newly described profibrotic IL-33/ST2/IL-13 pathway.