ЦЕНТАР ЗА МОЛЕКУЛСКУ МЕДИЦИНУ И ИСПИТИВАЊЕ МАТИЧНИХ ЋЕЛИЈА

„Galectin-3 and immunometabolism"

Nada Pejnovic
Professor in Pathophysiology, Faculty of Medical Sciences University of Kragujevac

Metabolism and immunity regulate internal homeostasis, but the molecular mechanisms that associate immune/inflammatory responses and metabolic disorders are incompletely understood. Obesity via gain of ectopic fat and by inducing complex immune/inflammatory response in metabolic tissues promote insulin resistance, hepatic steatosis, and β cell failure thus representing the major risk factor for type 2 diabetes mellitus (T2DM). Galectin-3 (Gal-3) is a multifunctional molecule that participates in a spectrum of diseases, including metabolic disorders and particularly diabetic complications via its receptor function for advanced glycation end-products (AGEs) and advanced lipoxidation end-products (ALEs). Gal-3 modulates a variety of cellular functions, as well as inflammation and fibrogenesis. Recently, we have demonstrated that Gal-3 have a protective role in the development of obesity and T2DM. We have shown that Gal-3 deficiency in mice leads to high-fat diet-induced excess adiposity, dysregulated glucose metabolism and insulin resistance, inflammation in adipose tissue and pancreatic islets, enhanced liver steatosis and less pronounced liver inflammation and fibrosis. In addition to its immuno-modulatory effects, Gal-3 might be involved in the regulation of adipose tissue and β cell function by yet unknown mechanisms. Our findings of increased expression of Gal-3 in islets upon high-fat dieting may be part of an adaptive response to tissue injury, favoring resolution of inflammation. Most recent data on the association of low plasma concentrations of Gal-3 with insulin resistance in patients with T2DM highlights its clinical importance.

Our future studies will address the unresolved role of Gal-3 in β cell function and islet inflammation in mice exposed to obesogenic diet using transgenic mice overexpressing Gal-3 specifically in the islets and Gal-3 knock-out mice. These studies will focus on the investigation of metabolic parameters, ectopic fat accumulation in pancreas, islet fibrosis, β cell dysfunction (β-cell mass, proliferation, apoptosis, insulin secretion), Gal-3 expression within islets (nuclear/cytoplasmatic, cell types), characterization of the immune cells that infiltrate the islets such as M1 and M2 macrophages, CD11bLy6C monocytes, DCs subpopulations, T and B lymphocytes, expression of IL-1β, TNF-α, IL-6, chemokines and their receptors on myeloid cells (CCR2, CCL2), NLRP3 inflammasome and anti-inflammatory cytokines IL-10 and IL-33 within islets. In addition, ALE/AGE-dependent effects in islets, RAGE expression in islets, the role of Gal-3 in trophic actions of incretins and Wnt/β-catenin signaling in protection of pancreatic beta cells from apoptosis using primary β cells exposed to proinflammatory stimuli, islets response to metabolic stimuli (high glucose, palmitate) and effects of soluble Gal-3 on β cell functions will be studied. Transcriptome analyses of pancreas, liver and gut for the genes related to immune response, inflammation, adhesion, apoptosis, fatty acid, lipids, cytoskeleton, ER, ion transport, NLRP3 inflammasome components, IL-1β, IL-18, IL-33 and apoptosis will be done using Affymetrix chip techniques in a UNIL core facility in Switzerland.