Galectin-3 Deficiency Accelerates High-Fat Diet–Induced Obesity and Amplifies Inflammation in Adipose Tissue and Pancreatic Islets

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Obesity-induced diabetes is associated with low-grade inflammation in adipose tissue and macrophage infiltration of islets. We show that ablation of galectin-3 (Gal-3), a galactoside-binding lectin, accelerates high-fat diet–induced obesity and diabetes. Obese *LGALS3*$^{-/-}$ mice have increased body weight, amount of total visceral adipose tissue (VAT), fasting blood glucose and insulin levels, homeostasis model assessment of insulin resistance, and markers of systemic inflammation compared with diet-matched wild-type (WT) animals. VAT of obese *LGALS3*$^{-/-}$ mice exhibited increased incidence of type 1 T and NKT lymphocytes and proinflammatory CD11c^{+}CD11b^{+} macrophages and decreased CD4^{+}CD25^{+}FoxP3^{+} regulatory T cells and M2 macrophages. Pronounced mononuclear cell infiltrate, increased expression of NLRP3 inflammasome and interleukin-1β (IL-1β) in macrophages, and increased accumulation of advanced glycation end products (AGEs) and receptor for AGE (RAGE) expression were present in pancreatic islets of obese *LGALS3*$^{-/-}$ animals accompanied with elevated phosphorylated nuclear factor-κB (NF-κB) p65 and mature caspase-1 protein expression in pancreatic tissue and VAT. In vitro stimulation of *LGALS3*$^{-/-}$ peritoneal macrophages with lipopolysaccharide (LPS) and saturated fatty acid palmitate caused increased caspase-1–dependent IL-1β production and increased phosphorylation of NF-κB p65 compared with WT cells. Transfection of *LGALS3*$^{-/-}$ macrophages with NLRP3 small interfering RNA attenuated IL-1β production in response to palmitate and LPS plus palmitate. Obtained results suggest important protective roles for Gal-3 in obesity-induced inflammation and diabetes. ***Diabetes*** **62:1932–1944, 2013**

Metabolic inflammation, "metaflammation," is a chronic, low-grade adipose tissue inflammation triggered by various metabolic "danger" signals during obesity that precedes the development of insulin resistance and type 2 diabetes (1). Adipose tissue–associated regulatory T cells (Tregs), type 2 T helper cells, and alternatively activated M2 macrophages protect from the instigation of nutrient excess–induced inflammation (2), whereas the recruitment of type 1 T helper lymphocytes and M1 macrophages and decreased Tregs in adipose tissue precede metabolic disorders (3,4). Proinflammatory interleukin-1β (IL-1β) and tumor necrosis factor-α impair insulin sensitivity, but molecular pathways that associate inflammation, diet, and type 2 diabetes are not fully understood (5). It has been postulated that the activation of nuclear factor-κB (NF-κB), a family of transcription factors that regulate the expression of proinflammatory genes upon cell stimulation with various factors including hyperglycemia and free fatty acids, is a molecular mechanism involved in insulin resistance (6). Most recently, the crucial role for the NLRP3 inflammasome, which consists of NLRP3 molecules, adaptor protein ASC, and procaspase-1 that catalytically activates caspase-1, causing the release of IL-1β and IL-18, was demonstrated in studies in which the ablation of the NLRP3 inflammasome prevented obesity-induced inflammation and insulin resistance (7–9).

Galectin-3 (Gal-3; also known as Mac-2), a 30-kDa β-galactoside–binding lectin, mainly located in the cytoplasm, but also in the nucleus, is expressed by a variety of cell types and regulates various T-cell functions and innate immune responses (10). Gal-3 plays an important disease-exacerbating role in autoimmune/inflammatory and malignant diseases (11–14). Gal-3 is also one of the pattern recognition receptors that bind and mediate the degradation of modified lipoproteins and advanced glycation end products (AGEs) (15). In contrast to other receptors for AGE (RAGEs), Gal-3 acts to protect from AGE-induced tissue injury. Therefore, Gal-3 ablation accelerates AGE-induced kidney injury in diabetes (16) and enhances atherogenesis (17). Gal-3 protects β-cells from the cytotoxic effect of IL-1β in rats (18) and its increased expression was demonstrated in islet endothelial cells in obesity-induced diabetes in mice (19).

The aim of this study was to investigate the role of Gal-3 in high-fat diet (HFD)–induced obesity and associated metabolic abnormalities by using mice lacking Gal-3 on a C57BL/6 background. We report here that Gal-3 ablation accelerated HFD-induced obesity and amplified inflammation in adipose tissue and pancreatic islets.

RESEARCH DESIGN AND METHODS

Experimental mice. Male Gal-3–deficient (*LGALS3*$^{-/-}$) mice on the C57BL/6 background and their littermate controls, wild-type (WT) C57BL/6 mice (6 weeks of age), obtained from the University of California Davis (Davis, CA; by courtesy of D.K. Hsu and F.T. Liu) were fed either a low-fat diet (LFD; 3% fat) or HFD (60% fat) obtained from Mucedola (Milano, Italy) for 11 or 18 weeks. All animal procedures were approved by the ethical committee (04/11) of the Faculty of Medical Sciences, University of Kragujevac.

Metabolic parameters. Body weights and fasting blood glucose levels were measured once every 2 weeks. Mice were fasted for 4 h, and glucose levels (mmol/L) were determined using the Accu-Chek Performa glucometer (Roche

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