

# LACK OF ST2 ENHANCES HIGH-FAT DIET-INDUCED VISCERAL ADIPOSITY AND INFLAMMATION IN BALB/c MICE

Jelena M. Pantic<sup>1</sup>, Nada N. Pejnović<sup>1,2</sup>, Gordana D. Radosavljević<sup>1</sup>, Ivan P. Jovanović<sup>1</sup>, Aleksandar L.J. Djukić<sup>2,3</sup>, Nebojsa N. Arsenijević<sup>1</sup>, and Miodrag L. Lukic<sup>1</sup>

<sup>1</sup>Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Serbia;

<sup>2</sup>Institute of Pathophysiology, Faculty of Medical Sciences, University of Kragujevac, Serbia;

<sup>3</sup>Center for Endocrinology, Diabetes, and Metabolic Diseases, Clinical Center Kragujevac, Serbia.

## DELECIJA GENA ZA ST2 PROMOVIŠE GOJAZNOST I INFLAMACIJU U VISCERALNOM ADIPOZNOM TKIVU BALB/C MIŠEVA NA DIJETI SA VISOKIM SADRŽAJEM MASTI

Jelena M. Pantic<sup>1</sup>, Nada N. Pejnović<sup>1,2</sup>, Gordana D. Radosavljević<sup>1</sup>, Ivan P. Jovanović<sup>1</sup>, Aleksandar L.J. Djukić<sup>2,3</sup>, Nebojsa N. Arsenijević<sup>1</sup>, and Miodrag L. Lukic<sup>1</sup>

<sup>1</sup>Centar za molekularnu medicinu i istraživanja matičnih ćelija, Fakultet medicinskih nauka, Univerzitet u Kragujevcu,

<sup>2</sup>Institut za patofiziologiju, Fakultet medicinskih nauka, Univerzitet u Kragujevcu,

<sup>3</sup>Centar za endokrinologiju, dijabetes i bolesti metabolizma, Klinički centar Kragujevac, Srbija

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### ABSTRACT

*Obesity and obesity-related disorders are strongly associated with a chronic low-grade inflammation that originates from growing visceral adipose tissue during nutrient excess. Although interleukin (IL)-33 may play a protective role in obesity and atherosclerosis, the impact of the IL-33/ST2 axis on metabolic disorders needs to be further elucidated.*

*In this study, we investigated the role of the IL-33/ST2 pathway in high-fat diet (HFD)-induced obesity using ST2-deficient (ST2<sup>-/-</sup>) and wild type BALB/c mice.*

*The deletion of ST2 enhanced systemic and visceral adipose tissue (VAT) inflammation; ST2<sup>-/-</sup> mice that were fed a HFD for 18 weeks had experienced a significantly increased weight gain and had a higher amount of total VAT. More classically activated M1 macrophages and markedly fewer alternatively activated M2 macrophages were observed in the VAT of the HFD-fed ST2<sup>-/-</sup> mice. Additionally, the VAT of the HFD-fed ST2<sup>-/-</sup> mice had an increased percentage of CD3<sup>+</sup> T cells but fewer CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> T regulatory cells when compared to the VAT of the low-fat diet-fed controls. The numbers of CD3<sup>+</sup>IL-17<sup>+</sup> and IL-5 positive VAT-derived mononuclear cells were significantly decreased in the HFD-fed ST2<sup>-/-</sup> mice. Serum levels of the proinflammatory cytokines IL-1 $\beta$  and IFN- $\gamma$  were increased in the HFD-fed ST2<sup>-/-</sup> mice, while the levels of IL-6 and CRP did not differ among the groups. Importantly, the levels of the anti-inflammatory cytokines IL-10 and IL-13 were significantly lower in the sera of the ST2<sup>-/-</sup> mice than the levels in the sera of the wild-type controls.*

*Our findings suggest a protective role of IL33/ST2 signaling in high-fat diet-induced adipose tissue inflammation. ST2 deficiency related to nutrient excess is associated with the polarisation of macrophages toward the M1 phenotype and the induction of a Th1-mediated immune response.*

**Key words:** obesity, adipose tissue, inflammation, cytokines, macrophages

### SAŽETAK

*U osnovi patogeneze gojaznosti i metaboličkih poremećaja povezanih sa gojaznošću je hronična sistemska inflamacija niskog stepena koja nastaje u visceralnom adipoznom tkivu (VAT) u uslovima povećanog unosa nutrijenata. Iako rezultati dosadašnjih istraživanja ukazuju na moguću protektivnu ulogu IL-33 u nastanku gojaznosti i ateroskleroze, uloga IL-33/ST2 signalnog puta u patogenezi ovih bolesti je nedovoljno razjašnjena.*

*U ovom istraživanju ispitivali smo ulogu IL-33/ST2 signalnog puta u mišjem modelu gojaznosti indukovane primenom dijeta sa visokim sadržajem masti u ST2 deficitarnih i miševima divljeg soja BALB/c.*

*Delecija gena za ST2 promoviše sistemska inflamaciju i inflamaciju u VAT-u što se ogleda u porastu telesne mase i uvećanju količine VAT-a tokom 18 nedelja primene dijeta sa visokim sadržajem masti. Proinflamatorni milje u VAT-u ST2<sup>-/-</sup> miševa na ishrani bogatoj mastima karakteriše povećana zastupljenost klasično aktiviranih M1 makrofaga, uz smanjeno prisustvo alternativno aktiviranih M2 makrofaga. Pored toga, dijeta sa visokim sadržajem masti značajno je uticala na povećanje zastupljenosti CD3<sup>+</sup> T limfocita, dok je prisustvo CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> regulatornih T limfocita bilo značajno sniženo u VAT-u ST2<sup>-/-</sup> miševa u odnosu na ST2<sup>-/-</sup> miševima na dijeti sa niskim sadržajem masti. Učestalost CD3<sup>+</sup>IL-17<sup>+</sup> i IL-5 pozitivnih mononuklearnih ćelija je bila značajno smanjena u VAT-u gojaznih ST2<sup>-/-</sup> miševa. Iako nije bilo razlike u serumskim nivoima IL-6 i CRP-a, koncentracija proinflamatornih citokina IL-1 $\beta$  i IFN- $\gamma$  je bila povećana u gojaznih ST2<sup>-/-</sup> miševa. Važno je istaći da su serumski nivoi anti-inflamatornih citokina, IL-10 i IL-13, bili niži u ST2<sup>-/-</sup> miševa u poređenju sa miševima divljeg soja.*

*Rezultati studije ukazuju na protektivnu ulogu IL-33/ST2 signalnog puta u pokretanju inflamacije u VAT-u nakon primene dijeta sa visokim sadržajem masti, koju karakteriše polarizacija makrofaga u pravcu M1 fenotipa i indukcija Th1 imunskog odgovora.*

**Ključne reči:** gojaznost, adipozno tkivo, inflamacija, citokini, makrofagi

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Correspondence to: Dr. Jelena M. Pantic, Faculty of Medical Sciences, University of Kragujevac; Svetozara Markovica 69, 34000 Kragujevac, Serbia;

Phone: +381641550001; e-mail: panticjelena@open.telekom.rs









