ST2 DEFICIENCY AMELIORATES HIGH FAT DIET-INDUCED LIVER STEATOSIS IN BALB/C MICE

Nemanja Jovicic [1,2*], Ilija Jeftic [1,3*], Marina Miletic Kovacevic [2], Irena Tanaskovic [2], Nebojsa Arsenijevic [1], Miodrag L. Lukic [1], Nada Pejnovic [1,3*]
[1] Center for Molecular Medicine;
[2] Institute of Histology;
[3] Institute of Pathophysiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

DELECIJA GENA ZA ST2 U BALB/C MIŠEVA UBLAŽAVA STEATOZU JETRE INDUKOVANU DIJETOM SA VISOKIM SADRŽAJEM MASTI

Nemanja Jovičić [1,2*], Ilija Jeftić [1,3*], Marina Miletić Kovačević [2], Irena Tanasković [2], Nebojša Arsenijević [1], Miodrag L. Lukić [1], Nada Pejnović [1,3*]
[1] Centar za molekulsku medicinu;
[2] Institut za histologiju;
[3] Institut za patofiziologiju, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija

Received / Primljen: 12. 02. 2015.

*The authors NJ and IJ contributed equally to this study.

Accepted / Prihvaćen: 24. 02. 2015.

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is strongly associated with obesity, but the molecular mechanisms of liver steatosis and its progression to non-alcoholic steatohepatitis and fibrosis are incompletely understood. Immune reactivity plays an important role in the pathogenesis of NAFLD. The IL-33/ST2 axis has a protective role in adiposity and atherosclerosis, but its role in obesity-associated metabolic disorders requires further clarification. To investigate the unresolved role of IL-33/ST2 signalling in NAFLD, we used ST2-deficient ($ST2^{-/-}$) and wild type (WT) BALB/c mice maintained on a high-fat diet (HFD) for 24 weeks. HFD-fed $ST2^{-/-}$ mice exhibited increased weight gain, visceral adipose tissue weight and triglyceridaemia and decreased liver weight compared with diet-matched WT mice. Compared with WT mice on an HFD, ST2 deletion significantly reduced hepatic steatosis, liver inflammation and fibrosis and downregulated the expression of genes related to lipid metabolism in the liver. The frequency of innate immune cells in the liver, including $CD68^+$ macrophages and $CD11c^+$ dendritic cells, was lower in HFD-fed $ST2^{-/-}$ mice, accompanied by lower TNFα serum levels compared with diet-matched WT mice. Less collagen deposition in the livers of $ST2^{-/-}$ mice on an HFD was associated with lower numbers of profibrotic $CD11b^+Ly6c^{low}$ monocytes and $CD4^+IL\text{-}17^+$ T cells in the liver, lower hepatic gene expression of procollagen, IL-33 and IL-13, and lower serum levels of IL-33 and IL-13 compared with diet-matched WT mice.

Our findings suggest that the IL-33/ST2 axis may have a complex role in obesity-associated metabolic disorders. Although it is protective in HFD-induced adiposity, the IL-33/ST2 pathway promotes hepatic steatosis, inflammation and fibrosis.

Key words: *Obesity, steatosis, non-alcoholic steatohepatitis, liver fibrosis, immune cells*

SAŽETAK

Nealkoholna masna bolest jetre je najčešće udružena sa gojaznošću, ali su molekularni mehanizmi razvoja steatoze i progresije u stetaohepatitis i fibrozu jetre nedovoljno razjašnjeni. Imunski mehanizmi imaju važnu ulogu u razvoju nealkoholne masne bolesti jetre. IL-33/ST2 signalni put ima zaštitnu ulogu u gojaznosti i aterosklerozi, ali je njegova uloga u razvoju metaboličkih poremećaja udruženih sa gojaznošću nedovoljno ispitana.

U ovom istraživanju ispitivali smo ulogu IL-33/ST2 signalnog puta u nealkoholnoj masnoj bolesti jetre na mišjem modelu gojaznosti indukovane primenom dijete sa visokim sadržajem masti u trajanju od 24 nedelje na ST2 deficijentnim ($ST2^{-/-}$) i miševima divljeg soja BALB/c.

$ST2^{-/-}$ miševi na dijeti sa visokim sadržajem masti su imali veći prirast telesne težine, veću težinu visceralnog masnog tkiva i više serumske nivoe triglicerida, dok je težina jetre bila manja u poređenju sa miševima divljeg soja na istoj dijeti. Nadalje, delecija $ST2^{-/-}$ gena je značajno smanjila steatozu jetre, inflamaciju i fibrozu jetre što je bilo praćeno sniženom ekspresijom gena uključenih u metabolizam lipida u jetri. Zastupljenost ćelija prirodne imunosti u jetri, $CD68^+$ makrofaga i $CD11c^+$ dendritskih ćelija i serumski nivo TNFα su bili niži kod $ST2^{-/-}$ miševa. Manje izražena fibroza jetre u $ST2^{-/-}$ miševa je bila povezana sa sniženom zastupljenošću profibrotskih $CD11b^+Ly6c^{low}$ monocita i $CD4^+IL\text{-}17^+$ T limfocita u jetri, sniženom ekspresijom gena za prokolagen, IL-33 i IL-13 i sniženim serumskim nivoima IL-33 i IL-13 u poredjenju sa miševima divljeg soja.

Dobijeni rezultati ukazuju na kompleksnu ulogu IL-33/ST2 signalnog puta u metaboličkim poremećajima udruženim sa gojaznošću. Iako protektivan za razvoj gojaznosti, IL-33/ST2 signalni put pospešuje steatozu, inflamaciju i fibrozu jetre.

Ključne reči: *gojaznost, steatoza, nealkoholni steatohepatitis, fibroza jetre, imunske ćelije*

DE GRUYTER OPEN

UDK: 616.36-008.9:577.2 / Ser J Exp Clin Res 2015; 16 (1): 9-20
DOI: 10.1515/SJECR-2015-0002

Corresponding author: Nada Pejnovic, MD, PhD, Professor of Pathophysiology, Institute of Pathophysiology, Faculty of Medical Sciences, University of Kragujevac, Svetozara Markovica 69, 34000 Kragujevac, Serbia
Tel: +381 34 306 800, Fax: +38134306800112, E-mail: nada.pejnovic@gmail.com