Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Protective role of IL-33/ST2 axis in Con A-induced hepatitis

Vladislav Volarevic[1], Marina Mitrovic[2], Marija Milovanovic[1], Ivanka Zelen[2], Ivana Nikolic[2], Slobodanka Mitrovic[3], Nada Pejnovic[1], Nebojsa Arsenijevic[1], Miodrag L. Lukic[1,*]

[1]*Department of Microbiology and Immunology, Centre for Molecular Medicine and Stem Cell Research, Faculty of Medicine, University of Kragujevac, Serbia;* [2]*Department of Biochemistry, Centre for Molecular Medicine and Stem Cell Research, Faculty of Medicine, University of Kragujevac, Serbia;* [3]*Department of Pathology, Centre for Molecular Medicine and Stem Cell Research, Faculty of Medicine, University of Kragujevac, Serbia*

See Editorial, pages 7–10

Background & Aims: We used Concanavalin A-induced liver injury to study the role of Interleukin 33 and its receptor ST2 in the induction of inflammatory pathology and hepatocellular damage.

Methods: We tested susceptibility to Concanavalin A induced hepatitis in ST2 deficient and wild type BALB/c mice and analyzed the effects of single injection of Interleukin 33 as evaluated by liver enzyme test, quantitative histology, mononuclear cell infiltration, cytokine production, intracellular staining of immune cells, and markers of apoptosis in the liver.

Results: ST2 deficient mice developed significantly more severe hepatitis and had significantly higher number of mononuclear cells in the liver, CD4+ and CD8+ T cells, NKp46+ and CD3+NKp46+ cells, and F4/80+ macrophages. The level of pro-inflammatory cytokines in the sera and number of TNF alpha, IFN gamma, and IL-17 producing cells was higher in ST2 deficient mice. In contrast, number of CD4+Foxp3+ cells was statistically higher in wild type mice. Additionally, treatment of wild type mice with single (1 μg) injection of Interleukin 33 led to attenuation of the liver injury and milder infiltration of mononuclear cells, increase in total number of liver CD4+Foxp3+ cells and IL-4 producing CD4+ T cells. Interleukin 33 also suppressed the activation of caspase 3, prevented the expression of BAX, and enhanced the expression of antiapoptotic Bcl-2 in the liver.

Conclusions: We concluded that Interleukin 33/ST2 axis downregulated Concanavalin A-induced liver injury and should be evaluated as potential target in fulminant hepatitis in humans.

Keywords: Interleukin 33; BALB/c mice; ST2 deficient mice; Concanavalin A; Hepatitis.

Received 25 November 2010; received in revised form 16 March 2011; accepted 18 March 2011; available online 18 May 2011

☆ DOI of original article: 10.1016/j.jhep.2011.05.007.

* Corresponding author. Address: Department of Microbiology and Immunology, Centre for Molecular Medicine and Stem Cell Research, Faculty of Medicine, University of Kragujevac, 69 Svetozara Markovica Street, 34000 Kragujevac, Serbia. Tel./fax: +381 34306800x112.

E-mail address: miodrag.lukic@medf.kg.ac.rs (M.L. Lukic).

Abbreviations: Con A, Concanavalin A; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; IL, interleukin; GM-CSF, granulocyte macrophage colony-stimulating factor; STAT1, signal transducer and activator of transcription 1; NK, natural killer; NKT, natural killer T cells; IL-1Racp, IL-1 receptor accessory protein; sST, secreted soluble 2 form; SECs, liver sinusoidal endothelial cells; $ST2^{-/-}$, ST2 deficient mice; WT, wild type mice; MNC, liver mononuclear cell; ALT, alanine aminotransaminase; AST, asparate aminotransferase; H&E, Hematoxylin and Eosin.

Introduction

Acute liver failure is associated with significant mortality and could be triggered by autoimmune hepatitis, viral hepatitis, alcohol consumption, and hepatotoxins. The underlying pathophysiological mechanisms are still incompletely understood and therefore therapeutic options are limited.

Concanavalin A (Con A)-induced liver injury is a well-established murine model of T-cell mediated hepatitis [1–4]. Intravenous injection of Con A induces acute liver injury and systemic immune activation in mice that resemble the pathology of immune mediated hepatitis in humans [5]. Activated T cells have a critical role in Con A-induced liver damage [6]. CD4+ T lymphocytes infiltrate the liver tissue and secrete large amount of tumor necrosis factor (TNF) alpha, interferon (IFN)-gamma, interleukin (IL)-2, interleukin (IL)-6, and granulocyte macrophage colony-stimulating factor (GM-CSF) [7–9]. Con A-induced liver damage is largely dependent on Th1 cytokines [7,10] as IFN gamma and signal transducer and activator of transcription 1 (STAT1)-deficient mice are resistant to Con A-induced hepatitis. Apart from $CD4^+$ T cells, CD8+ T cells, natural killer (NK), natural killer T (NKT) cells, and macrophages could induce hepatocyte cell death by either cell to cell contact, secretion of pro-inflammatory cytokines or reactive oxygen species [5,7,11,12].

IL-33 is a member of the IL-1 cytokine family that interacts with a heterodimeric receptor comprising ST2 and IL-1 receptor accessory protein (IL-1Racp) [13]. The *ST2* gene encodes two protein isoforms: ST2L, a transmembrane receptor; and a secreted soluble ST2 form, which is a decoy receptor for IL-33 [14–17]. IL-33 upon binding to ST2 on Th2 lymphocytes leads to secretion of interleukin (IL)-4, interleukin (IL)-5, interleukin (IL)-13, and interleukin (IL)-10 [13–18] thus balancing Th1 immune response [16]. IL-33 reduces atherosclerosis by promoting Th2-type immune responses [19]. However, IL-33 can also mediate atopic dermatitis and anaphylaxis by mast cell activation [19]. More