

## Editorial

# Interleukin-33 and its Soluble Receptor ST2 as Non-Invasive Biomarkers of Human Hepatitis

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The cytokine interleukin-33 (IL-33) is a member of IL-1 family described in 2005 with pluripotent functions in various diseases and wide spectrum of target immune cells in tissues [1]. In human, IL-33 is encoded on chromosome 9 and full length IL-33 is synthesized from two mRNA transcripts translating into one IL-33 protein composing of 270 amino acids [2]. Evolving data evidenced “two lives” of IL-33 due to its unique nuclear localization as nuclear repressor and extracellular cytokine functions (danger signal, immune defense, tissue repair and skewing of T helper cell responses). Primarily, IL-33 was reported to be present in tissue barrier cells (vascular endothelial cells, epithelial cells) as guardian of barriers but later on it was found to be localized/expressed by parenchymal cells such as astrocytes, adipocytes and hepatocytes [3]. The release of IL-33 as an “alarmin” from these cells was described to be linked with cellular demise (apoptosis, necrosis, necroptosis) by infection, injury, mechanical stress or trauma. In contrast to alarmin functions, the expression of IL-33 was associated with chronic diseases as well. Therefore, IL-33 evolved as a biomarker of acute and chronic diseases. As reviewed recently, the extracellular IL-33 is prone to cleavage by enzymes such as caspases-(1/3/7), elastase, chymase, calpain and cathepsin G which limits the alarmin signals and degrades the biological activity of IL-33 [3,4]. Another study demonstrated inactivation of IL-33 by structural changes or formation of disulfide bonds upon oxidation of IL-33 protein molecule [5]. The extracellular cytokine functions of IL-33 are orchestrated by interaction with dimeric IL-1RAcP/ST2L receptors. The IL-33 specific ST2-receptor is mainly expressed by immune cells such as Th2 cells, nuocytes/innate lymphoid cells (ILCs), granulocytes, macrophages and CD8 T cells [3,4]. The soluble ST2 (sST2) receptor acts as decoy receptor of IL-33 and it abrogates the activity of circulating IL-33. However, the level of sST2 was associated with various diseases as indicator of disease process.

In human liver pathology, we first evidenced the over-expression of IL-33 in liver sinusoidal endothelial cells and vascular endothelial cells in fibrotic human livers [6]. Accumulating data demonstrated association of circulating levels

of IL-33 or sST2 with clinical human liver diseases which poised the role of soluble IL-33/ST2 as biomarkers of hepatitis to discern different stages of hepatitis. Serum IL-33 was elevated in human patients (mean values) of acute liver failure (~190 pg/ml), acute-on-chronic liver failure (~200 pg/ml) and chronic liver failure (~110 pg/ml) than healthy control (HC) (~25 pg/ml) [7]. In a cohort of HC and chronic hepatitis C (CHC) patients in Italy, IL-33 level was raised in CHC (350-430 ng/ml) than HC (30-60 ng/ml), moreover, IL-33 level (180-320 ng/ml) varied in early stage of liver fibrosis (F1-F2 METAVIR score) than late stage (F3-F4) of fibrosis (450-550 ng/ml) [8]. Post antiviral treated patients showed lower level of IL-33 in serum indicating a prognostic value of IL-33 (8). Up-regulated circulating level of IL-33 was found in chronic hepatitis B (30-70 pg/ml) and CHC (210-900 pg/ml) affected Chinese patients than HC (10-25 pg/ml) which lowered to 20 pg/ml following 12 weeks of antiviral therapy [9,10]. In hepatocellular carcinoma (HCC) patients, serum IL-33 level raised during metastasis (137 pg/ml mean value) or pre-operative HCC (116 pg/ml) than non-metastatic conditions (8 pg/ml) or HC (4 pg/ml) individuals [11]. In infants with biliary atresia, IL-33 increased in sera of children (791 pg/ml) than HC infants (588 pg/ml) and it positively correlated with gamma-glutamyl transferase level [12]. In visceral leishmaniasis (hepatotropic parasite) infection in human, the IL-33 level was up-regulated (41 pg/ml) than HC (8 pg/ml) [13] suggesting IL-33 as a marker of wide range of liver diseases. The IL-33 level was significantly increased (57-75 pg/ml) in sera of primary biliary cirrhosis patients than HC (32 pg/ml) suggesting IL-33 a diagnostic marker of biliary disease [14]. In HBV infected acute-on-chronic liver failure (ACLF) human patients, the serum IL-33 was raised (313 pg/ml) than chronic hepatitis B (97 pg/ml) or HC (28 pg/ml) groups highlighting the use of IL-33 to discern different stages of viral hepatitis [15]. In chronic HBV infection and in ACLF, significantly higher IL-33 serum concentration was detected (14 pg/ml; 17 pg/ml respectively) compared to HC (5 pg/ml), however, in this study the level of soluble IL-33 was lower than other studies which may be associated with inclusion of more male patients in this study or difference of ELISA kit

used [16,17]. In patients with HCC in Germany, serum IL-33 level (1079 pg/ml) was raised in comparison to HC (218 pg/ml) but not in liver cirrhosis (203 pg/ml), however, IL-33 level in HCC was higher due to HCV or alcohol abuse than HBV infection [18].

The serum sST2 was elevated in human patients (mean values) of acute liver failure (~1910 pg/ml), acute-on-chronic liver failure (~1750 pg/ml) and chronic liver failure (~280 pg/ml) than HC (~50 pg/ml) [7]. In HCC and liver cirrhosis patients sST2 level was up-regulated (741 pg/ml; 1653 pg/ml respectively) than HC (38 pg/ml) [18] with non-significant difference in level of sST2 during HCC/liver cirrhosis induced by HBV, HCV or alcohol [18]. The sST2 level in serum was significantly raised in chronic HBV and HCV patients (12500 pg/ml; 2000-2400 pg/ml respectively) than HC (900-1000 pg/ml) indicating the differential expression with type of viral infection [9,10]. The soluble sST2 level predicted mortality in HBV related ACLF in a cohort of Chinese population with increased sST2 concentration in ACLF (94 ng/ml) and chronic HBV infection (19 ng/ml) than HC (9 ng/ml), however, the level of soluble IL-33 did not vary in these groups [19]. The sST2 level was significantly augmented (1343-1439 pg/ml) in sera of primary biliary cirrhosis patients than HC (144 pg/ml) revealing sST2 as good indicator of biliary disease [14]. In HBV infected ACLF patients, sST2 was raised (1545 pg/ml) than chronic hepatitis B (152 pg/ml) or HC (149 pg/ml) groups highlighting sST2 differentiating marker of viral hepatitis [15]. In liver fibrosis caused by HBV, significantly increased level of sST2 (1133 pg/ml) predicted the progression of liver fibrosis in comparison to HC (762 pg/ml) individuals [20].

## CONCLUSION

The ELISA based clinical data strongly evidenced that soluble IL-33 or sST2 can be used as non-invasive diagnostic or prognostic biomarkers of liver diseases. However, variation in results of serum IL-33/sST2 concentration is associated with type of viral hepatitis, liver pathology or stage of liver disease. In future, further studies and considerations of sensitivity, specificity, reproducibility and widespread availability (non-patented) will be needed to finally accredit the IL-33/sST2 as biomarkers of hepatitis.

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