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Review

The Dynamic Role of the IL-33/ST2 Axis in Chronic Viral-infections: Alarming and Adjuvanting the Immune Response

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ABSTRACT

Interleukin 33 (IL-33), a member of the IL-1 family, is constitutively expressed in epithelial and in endothelial cells at barrier sites, acting as a danger signal and adjuvanting the immune response following tissue damage and infection. Originally implicated in allergy, IL-33 is also known to be involved in innate and adaptive immune responses by enhancing natural killer, Th1, and CD4 and CD8 T-cell functions. The nature of the antiviral immune response orchestrated by IL-33 depends on the site of infection, the duration of the disease and the cytokine milieu. In this review, we focus on the distinctive contribution of IL-33 as an anti-infective and proinflammatory cytokine in response to cell death and viral infections. The dynamic role of IL-33 in the acute and chronic phases of infection with HIV, hepatitis B and C viruses, and with CMV is highlighted. This review will also discuss the potential immunotherapeutic and adjuvant roles of IL-33.

Search Strategy and Selection Criteria: English language, indexed publications in PubMed were searched using combinations of following key words: "interleukin-33", "IL-33", "suppression of tumorigenicity 2", ST2", "sST2", "HIV", "HBV", "HCV", "CMV", "HPV", "immunotherapy" and "vaccine". Except for seminal studies, only articles published between 2010 and 2016 were included.

Contents

1. Introduction: A Decade-old Cytokine

In 2005, Schmitz et al. identified interleukin-33 (IL-33), a 30 kDa nuclear cytokine that belongs to the IL-1 family (Schmitz et al., 2005) and that acts as an "alarmin" in response to the cellular damage induced by stress or by infection (Cayrol and Girard, 2014, Moussion et al., 2008). IL-33 is constitutively expressed within the nucleus of endothelial and

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of epithelial cells, particularly in tissue barrier sites and in fibroblastic reticular cells of the lymph nodes and of the spleen, in which this cytokine contributes to the maintenance of mechanical barriers (Moussion et al., 2008, Martin and Martin, 2016, Schmitz et al., 2005, Peine et al., 2016, Cayrol and Girard, 2014). Furthermore, IL-33, which is released by damaged endothelial and epithelial cells at barrier sites, functions as a damage-associated molecular pattern (DAMP) to trigger activated T-cells, either indirectly through proinflammatory cytokine production by innate immune system cells, or directly in a TCR-independent manner by binding to pattern recognition receptors (PRRs) on T-cells, as recently reviewed (Peine et al., 2016). T-cells can also directly respond to IL-33 *via* its cognate suppressor of tumorigenicity 2 (ST2) receptor (Smithgall et al., 2008, Peine et al., 2016). IL-33 mainly targets mast cells, basophils, dendritic cells (DCs), macrophages, natural killer (NK) cells, group 2 innate lymphoid cells (ILC2) and T helper 2 (Th2) cells, all of which express ST2 (Jovanovic et al., 2012, Martin and Martin, 2016, Miller, 2011). The ST2 receptor to which the biologically active form of IL-33 binds is a complex consisting of the full-length, transmembrane isoform of ST2 (ST2L), in association with the IL-1 receptor accessory protein (IL-1rap); this receptor complex is expressed at barrier sites and also on certain peripheral blood mononuclear cells including the mast cells, NK cells and Th2 cells (Martin and Martin, 2016, Molofsky et al., 2015a). Conversely, the extracellular IL-33 that is released following cell damage is cleaved in a caspase-dependent and -independent manner, and also undergoes extracellular cysteine oxidation, all of which reduce the efficacy and half-life of IL-33. However, some isoforms of full length extracellular IL-33 and spliced variants of mature IL-33 still possess biological activity (Villarreal and Weiner, 2015, Cayrol and Girard, 2014, Cayrol and Girard, 2009). Moreover, the activity of extracellular IL-33 is controlled by its binding to the soluble form of ST2 (sST2), which serves as a decoy receptor to locally limit 'off target' IL-33 activity, thus avoiding inappropriate inflammatory responses (Kakkar and Lee, 2008) Fig. 1.

IL-33 was originally found to play a role in innate immunity and in the Th2 response involved in tissue repair following allergic reactions and helminthic infections (Lu et al., 2015). It is now known that IL-33 is also a crucial costimulator in the adaptive immune response, amplifying the responses of antiviral cytotoxic T lymphocytes (CTLs); IL-33 thus acts as an adjuvant (Villarreal et al., 2015b). Furthermore, Schiering et al. have shown that in mice, ST2 is preferentially expressed on colonic Treg cells, thereby allowing IL-33 to promote Treg function by inducing transforming growth factor (TGF)-β1-mediated differentiation of these cells in an inflammatory environment (Schiering et al., 2014).

More recently, IL-33 was shown to enhance the differentiation programs of diverse T-cell subsets including Th1, Th2, and Treg cells *via* the induction of their respective master regulator transcription factors T-bet, GATA-3 and Foxp3, in addition to inducing their specific signal transducer and activator of transcription (STAT) proteins (Peine et al., 2016). Furthermore, IL-33 was reported to amplify the inflammatory effects of differentiated Th1 and Th2 cell cultures in conjunction with IL-18, another IL-1 family member (Blom and Poulsen, 2012, Samarani et al., 2016).

In contrast to its constitutive expression on ILC2, Treg and Th2 cells, ST2 expression on Th1 cells is transient and contributes to virus-specific CD4 T-cell expansion, Th1 effector differentiation, and antiviral cytokine production (Molofsky et al., 2015a, Schmitz et al., 2005). Baumann et al. have shown that ST2 is induced on Th1 effector cells upon differentiation both *in vitro* and *in vivo* following lymphocytic choriomeningitis virus (LCMV) infection (Baumann et al., 2015). In Th1 cells, STAT4 and T-bet cooperate to drive ST2 expression. The absence of ST2 on CD4 T-

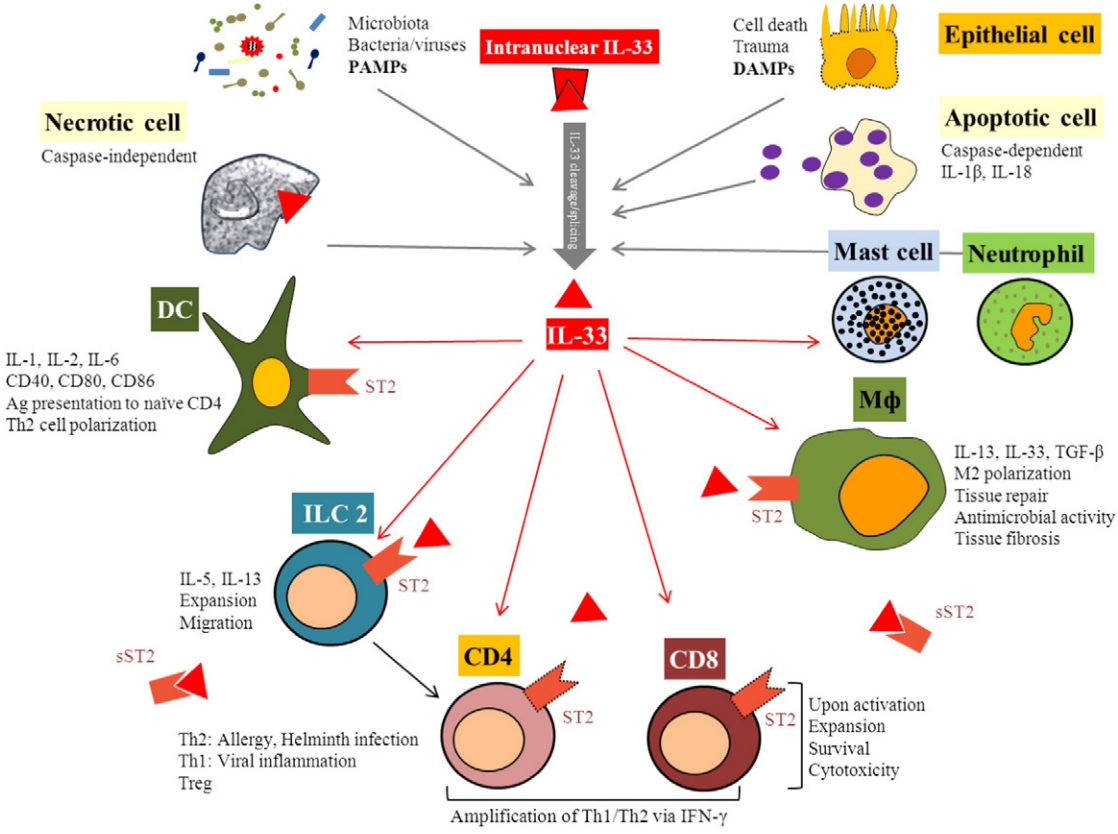

Fig. 1. Schematic representation of the induction of the IL-33/ST2 axis and its role in innate and adaptive immune responses. Intracellular IL-33 is released by apoptotic and necrotic epithelial cells and can undergo cleavage/splicing by enzymes secreted by mast cells and by neutrophils to generate the active form of IL-33. ST2 expressing cells are targeted by IL-33 to induce inflammatory and tissue healing effects. The induction of ST2 expression by CD4 and CD8 T-cells results in their expansion and survival. An array of cytokines is implicated in the functions of the IL-33/ST2 axis. Abbreviations: MΦ: macrophage; DC: dendritic cell; ILC2: group 2 innate lymphoid cells; Ag: antigen; IL-33: interleukin-33; ST2: suppressor of tumorigenicity2; sST2: soluble ST2; Treg: regulatory T-cell.

cells impairs Th1 cell activation during viral infection and results in decreased expansion, impaired effector function, and reduced T-cell–mediated immunopathology.

Molofsky et al. recently delineated the dynamic role of the IL-33/ST2 axis during microbial invasion with respect to the loss of epithelial integrity at damaged barrier sites (Molofsky et al., 2015b). Following an acute infection causing tissue injury, IL-33 synergized with other epithelial cytokines and chemokines to induce remodeling and to promote tissue homeostasis and repair. However, during chronic infection, a "conversion phase" occurs during which a massive release of IL-33 overwhelms the local regulation mediated by sST2, leading to an inflammatory response that in turn promotes NK, Th1 and cytotoxic CD8 T-cell responses (Bonilla et al., 2012, Molofsky et al., 2015a, Molofsky et al., 2015b, Cao et al., 2016). Over time, this persistent inflammation during chronic infection induces tissue damage and fibrosis (Li et al., 2014a).

The IL-33/ST2 axis has been reported to play a role in an increasing number of conditions associated with either tissue necrosis, as in the case of cardiac insufficiency and atherosclerosis (Miller et al., 2008, Miller, 2011), or with breached barriers as in the case of asthma (Li et al., 2014a, Salter et al., 2016), graft *vs.* host disease (GVHD) (Reichenbach et al., 2015, Vander Lugt et al., 2013), biliary cirrhosis (Volarevic et al., 2012, Sun et al., 2014), ulcerative colitis (UC) and Crohn's disease (CD) (Pastorelli et al., 2010). A role for the IL-33/ST2 axis has also been reported in autoimmune diseases such as systemic lupus erythematosus (SLE) (Li et al., 2014b) and rheumatoid arthritis (RA) (Tang et al., 2013), and in different allergic conditions (Cayrol and Girard, 2014, Hayakawa et al., 2007, Nygaard et al., 2016, Salter et al., 2016). Plasma levels of sST2, which are an indirect measure of IL-33 activity, have been used to predict disease outcome and/or to monitor treatment response in a number of conditions including cardiac insufficiency and colitis (Andersson et al., 2016). More recently, the IL-33/ST2 axis was implicated in septic shock (Alves-Filho et al., 2010), and in infections with Dengue virus (Becerra et al., 2008), *Toxoplasma gondii* (Jones et al., 2010), and *Pseudomonas aeruginosa* (Hazlett et al., 2010).

Collectively, these lines of evidence suggest that the IL-33/ST2 axis plays a key role in inducing tissue repair when barriers are breached, by alarming and enhancing immune responses in diverse conditions including cardiac insufficiency, autoimmune conditions, colitis, and infections.

The molecular and cellular roles of the IL-33/ST2 axis in animal and in human health and disease have been recently reviewed (Jovanovic et al., 2012, Cayrol and Girard, 2014, Rostan et al., 2015, Peine et al., 2016). Herein, we highlight the dynamic role of the IL-33/ST2 axis in the innate and adaptive immune responses that occur during acute and chronic infections, with a focus on HIV, hepatitis B and C viruses (HBV and HCV) and cytomegalovirus (CMV). We also discuss the IL-33/ST2 axis as a potential therapeutic target.

2. HIV Infection and the IL-33/ST2 response: Sounding the Alarm

Given that IL-33 is rapidly released from damaged cells following tissue damage, necrosis and activation of the inflammasome (Martin and Martin, 2016), it has been suggested that IL-33 may play a role in the pathogenesis of HIV infection (Barouch et al., 2016). In 2011, Miyagaki et al. were the first to report elevated sST2 levels in HIV-infected patients and in uninfected patients with skin barrier damage due to atopic dermatitis, compared to healthy controls (Miyagaki et al., 2011). Additionally, they observed reduced plasma levels of IL-33 in HIV-infected patients independently of the severity of their infection, in contrast to patients with atopic dermatitis. However, the dysregulated plasma levels of sST2 and of IL-33 did not correlate with age, eosinophil count or with other clinical parameters, which could be due to the small sample size of the study. In contrast, Secemsky et al. reported that 332 long-term antiretroviral therapy (ART)-treated HIV-infected patients had similar sST2 levels compared to age- and sex-matched controls (Secemsky et al., 2015). The aim of this study was to assess and to compare plasma sST2 levels with novel cardiovascular disease biomarkers such as growth differentiation factor 15 (GDF-15) and troponin I, in addition to established biomarkers such as C-reactive protein (CRP), D-dimer, IL-6 and cystatin C (Table 1). Despite non-elevated ST2 mean levels, sST2 and GDF-15 were predictors of cardiac insufficiency and of all-cause mortality in ART-treated patients, consistent with previous reports of uninfected individuals (Chen et al., 2013). Furthermore, Fitch et al. recently reported elevated ST2 levels as a marker of myocardial fibrosis in asymptomatic HIV-infected patients (Fitch et al., 2016). However, it should be noted that in both of these studiess of treated, HIV-infected individuals, single cross-sectional assessments of each biomarker were made.

HIV-associated gut barrier dysfunction and immune activation, which have been observed to occur early in infection, represent independent predictors of morbidity and mortality (Ponte et al., 2016, Hunt et al., 2014). The initiation of ART during chronic infection can reduce, but not normalize, barrier dysfunction and immune activation (Ananworanich et al., 2015, Hunt et al., 2014). We and others have reported that when ART is initiated immediately following HIV infection, plasma levels of gut damage markers remain elevated, in contrast to markers of cellular activation and of inflammation, which decrease significantly (Jenabian et al., 2015, Ananworanich et al., 2015). Our prospective analysis failed to detect a significant reduction in sST2 levels in patients initiating ART during the early phase of HIV infection, while long-term treatment initiated during the chronic phase normalized sST2 levels (Mehraj et al., 2016). Importantly, we determined the alarmin contribution of the IL-33/ST2 axis to the immune response by reporting a correlation of elevated sST2 levels with the CD8 T-cell count and with T-cell activation in the absence of a correlation with the plasma viral load. Thus, the immune response following acute infection characterized by increased numbers of CD8 T-cells and increased activation of these cells was associated with elevated sST2 levels, in response to 'the alarm'. The elevated sST2 levels correlated with indoleamine 2,3-dioxygenase enzyme activity and IFN-γ levels, both of which are implicated in Th1/Th2 regulation. Our findings in HIV-infected individuals support those reported by Baumann et al. of a murine lymphocytic choriomeningitis virus (LMCV) model in which IL-33 induced and enhanced Th-1 responses (Baumann et al., 2015). Furthermore, during acute HIV infection, sST2 levels correlated with the levels of intestinal fatty acid binding protein (I-FABP) and of sCD14, markers of gut epithelial damage and of microbial translocation, respectively. These observations establish a link between sST2 and gut tissue damage. Interestingly, these associations were lost during chronic HIV infection, suggesting a phase-dependent and transient role for the IL-33/ST2 axis in disease progression (Fig. 2). Moreover, IL-33, in conjunction with long-term TGF-β stimulation, has been shown to be associated with the development of fibrosis in a murine model of bleomycin-induced fibrosis (Li et al., 2014a). Gao et al. recently showed that in a murine model of diet-induced nonalcoholic steatohepatitis, IL-33 treatment prevented steatosis, while inducing fibrosis, in a ST2-dependent manner (Gao et al., 2016). Furthermore, in patients with either chronic obstructive pulmonary disease or with idiopathic pulmonary fibrosis, IL-33 is involved in the induction of lung fibrosis in bronchial epithelial cells *via* the induction of IL-6 and IL-8 (Shang et al., 2015). It is well established that during the chronic phase of HIV infection, collagen deposition in lymphoid tissues including Peyer's patches in the gut disrupts the T-cell zone and limits the number of resident CD4 T-cells (Schacker et al., 2005). The development of fibrosis is an important issue given that the level of lymphatic tissue collagen deposition foretells the magnitude of CD4 T-cell recovery following ART initiation. Thus, after sounding the alarm, the IL-33/ST2 axis may contribute to the development of fibrosis during the chronic phase of HIV infection (Fig. 2).

Collectively, these findings suggest a role for ST2 in HIV pathogenesis; this process is probably driven by HIV-induced damage to gut epithelial cells during the early, asymptomatic phase of infection. These findings also suggest that ST2 might be used as a surrogate marker of Th1 cell activation. More research is needed to confirm a direct link

Table 1
Studies assessing IL-33/ST2 dysregulation in the context of human infection with HIV, HBV and HCV.

Ref.	Infection	Tissue/organ/methods	Sample size (n)	Principal findings on IL-33/ST2 axis	Correlations/associations with IL-33/ST2 axis	Comments
Miyagaki et al. (2011)	HIV	Serum ELISA	26 → HIV; 28 → AD; 21 → C	sST2 levels increased but IL-33 levels decreased in HIV patients.	No correlation of sST2 or IL-33 with age, eosinophil count or other clinical measurements.	First report of IL-33/ST2 in HIV infection
Yndart et al. (2015)	HIV	Cell culture and *in vitro* infection ELISA qPCR, WB caspase assay	3 independent experiments	HIV-1 clade B causes increases in IL-33/ST2L expression	IL-33/ST2 expression led to increased expression of inflammatory genes and apoptosis in neuronal cells.	No such associations with HIV-1 clade C infection.
Secemsky et al. (2015)	HIV	Serum biomarkers and ECG and mortality data	332 → HIV 50 → C	ST2 and GDF-15 independently predicted cardiovascular dysfunction and all-cause mortality.	ST2 was the only factor predictive of diastolic dysfunction.	ST2 was not elevated in chronic HIV infected patients.
Mehraj et al. (2016)	HIV	Plasma and PBMCs ELISA FC qPCR	153 → HIV (48 EHI, 61 CHI, 23 CHI-ART, 21 EC) 20 → C	sST2 plasma levels were elevated in early HIV infection independent of age, sex, BMI, creatinine, cholesterol and CRP levels.	sST2 correlated with markers of gut damage, microbial translocation and immune activation.	No such associations were found in chronic HIV infection. IL-33 levels were not modulated.
Marvie et al. (2010)	HBV/HCV	Human liver biopsies, mice liver fibrosis model, qPCR, cell culture, ELISA, WB, IHC	34 → HCC 6 → C	IL-33 and ST2 mRNA levels increased in fibrotic liver in humans and mice	IL-33 correlated with ST2. IL-33 correlated with collagen synthesis in liver. Endothelial and stellate cells were the major sources of IL-33. T-cell expressed ST2.	IL-33/ST2 levels in HCC were similar to controls.
Wang et al. (2012a)	HBV	Serum and *in vitro* infection assays, ELISA, CBA	33 → CHB 20 → C	IL-33 and sST2 serum levels increased in CHB at the baseline.	IL-33 levels did not correlate with AST and ALT. IL-33 was associated with viral DNA inhibition *in vitro*. No correlation between sST2 and IL-33 levels.	IL-33 levels decreased with 12 weeks of adefovir dipivoxil therapy
Lei et al. (2015)	HBV	Serum, liver biopsies, ELISA, IHC	48 → ACLF 12 → CHB 16 → C	sST2 but not IL-33 was increased in HBV-ACLF	sST2 levels did not correlate with IL-33, TNF-α, IFN-γ and IL-10.	sST2 levels predicted disease severity and mortality
Gao et al. (2015)	HBV	Serum ELISA	60 → ACLF-HBV 58 → CHB 30 → C	IL-33 and ST2 serum levels were elevated in patients with HBV associated ACLF.	In ACLF-HBV, IL-33 levels significantly correlated with ALT levels, while sST2 levels significantly correlated with total bilirubin, HBV viral load and model for end-stage liver diseases. Elevated sST2 levels also predicted poor survival.	In all participants, serum IL-33 was significantly correlated with sST2.
Wang et al. (2012b)	HCV	Serum ELISA, CBA	154 → CHC 24 → SR-HCV 20 → C	IL-33 and sST2 serum levels increased in CHC	IL-33 levels correlated with AST and ALT in CHC No correlation between sST2 and IL-33 levels	IL-33 levels decreased with 12 weeks of IFN therapy

Abbreviations: HIV = Human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; AD = atopic dermatitis; IL-33 = interleukin-33; GDF-15 = growth differentiation factor 15; PBMCs = peripheral blood mononuclear cells; EHI = Early HIV Infection; CHI = chronic HIV infection; ART = antiretroviral therapy; EC = Elite controller; BMI = body mass index; CRP = C-reactive protein; CHC = chronic hepatitis C; SR-HCV = spontaneously resolved HCV; C = controls; HCC = hepatocellular carcinoma; CHB = chronic hepatitis B; IFN = interferon; ELISA = Enzyme-linked immunosorbent Assay; CBA = Cytometric Bead Array; WB = Western Blot; ECG: Echocardiograms; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ACLF = acute on chronic liver failure; IHC = Immunohistochemistry; FC = flow cytometry; qPCR = quantitative polymerase chain reaction.

between the IL-33/ST2 axis and Th1/Th2/Th17 alterations in the gut, and with the Th1 response *ex vivo*, in HIV infection, as observed in the murine LCMV model (Liang et al., 2015).

Upregulation of the IL-33/ST2 axis in the central nervous system (CNS) has also been reported to be associated with neurocognitive changes in HIV infection (Yndart et al., 2015). Specifically, IL-33 overexpression was associated with decreased synaptic function, increased apoptosis, and neuroinflammation in HIV-1 clade B infected CNS cell cultures. These results further support a role for dysregulation of the IL-33/ST2 axis in HIV infection.

IL-33 and IL-18, another member of the IL-1 family, are both processed by the inflammasome (Petrasek et al., 2012). Inflammasomes, the signaling platforms that detect pathogenic microorganisms and sterile stressors, are activated *via* protease caspase-1, IL-1β and IL-18 (two pro-inflammatory cytokines), and to a lesser extent, *via* IL-33 (Latz et al., 2013). Importantly, HIV-1 infection and inflammasome assembly are at play since many pathogen-associated molecular patterns (PAMPs) are derived from the virus' envelope, capsid, RNA, and reverse-transcribed DNA. The PAMPs and DAMPs produced by the destruction of infected CD4 T-cells and of damaged gut epithelial cells activate several pattern recognition receptors (PRRs) that include toll like receptors (TLRs), C-type lectin-like receptors (CLRs), RIG-like receptors (RLRs) and node-like receptors (NLRs), all of which contribute to the activation of transcription factors, such as NF-kB, that induce the expression of type-1 interferons, pro-inflammatory cytokines such as IL-1β and IL-18, and chemokines. HIV also activates different NLRs which results in the assembly of an inflammasome, the activation of caspase-1, and in the processing and release of IL-1 family cytokines (Samarani et al., 2016).

The contribution of the inflammasome to early SIV pathogenesis have been recently identified in necropsy studies of rhesus monkeys; these studies revealed that components of the inflammasome were triggered by SIV both at the site of inoculation and at early sites of distal virus spread as soon as 24 h post-infection (Barouch et al., 2016). We and others have previously shown increased levels, compared to healthy controls, of serum IL-18 in HIV-infected individuals; these levels were inversely correlated with the numbers of various NK cell subsets (Ahmad et al., 2002, Iannello et al., 2009); these cells express ST2 and are also targets of IL-33. A recent study of a murine model of CMV infection showed that NK cell expansion was mediated by ST2, with beneficial anti-viral effects (Nabekura et al., 2015). Thus, the individual and potential synergistic effects of IL-18 and of IL-33 at tissue barrier sites and in the blood warrant further investigation.

3. The IL-33/ST2 Axis in Viral Hepatitis: Creating Damage by Inducing Liver Fibrosis

Imbalances in the Th1/Th2 response were first implicated in the pathogenesis of hepatic failure induced by acetaminophen, mushroom

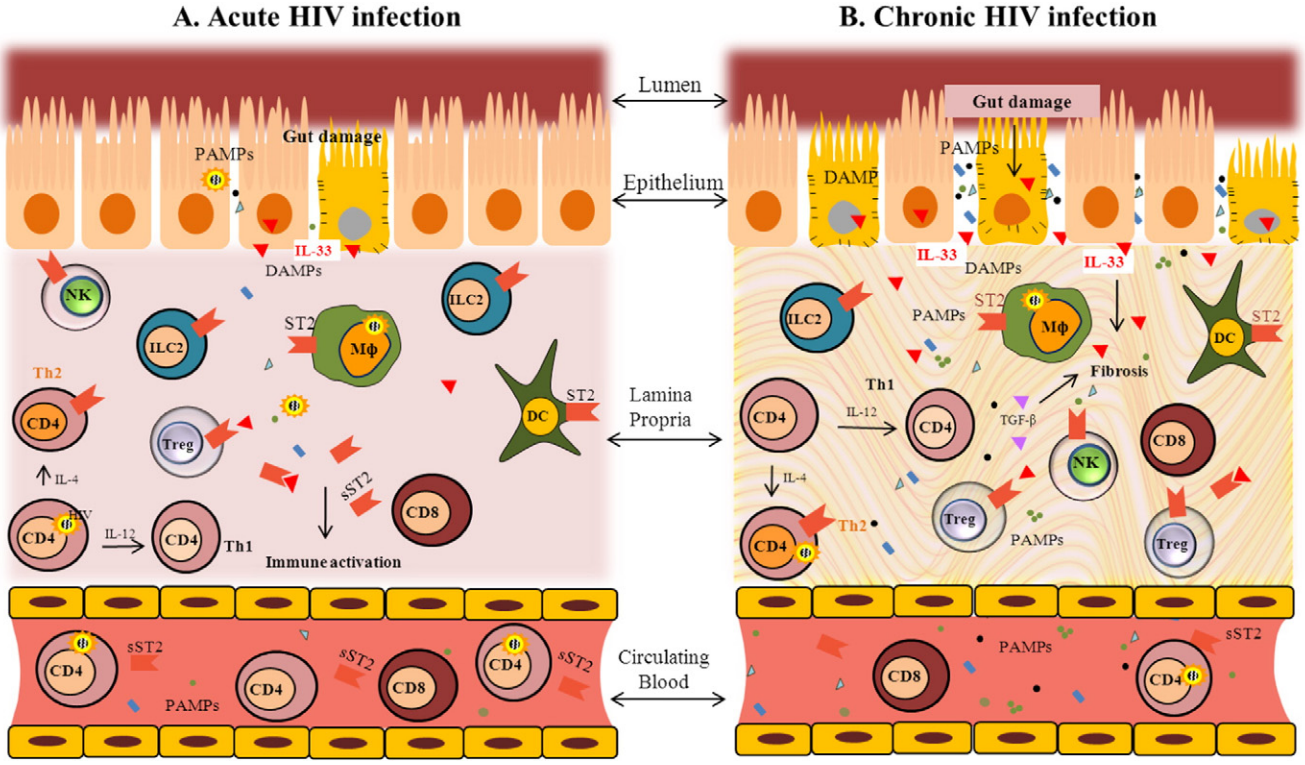

Fig. 2. IL-33/ST2 axis plays a dual role in gut epithelial homeostasis and immune activation during chronic viral infections. This figure depicts HIV infection as a model of acute and chronic phases of infection. A: During acute HIV infection, PAMPs and epithelial gut damage lead to the release of IL-33 which acts as a DAMP to alert the immune system. Expression of IL-33 receptor ST2 is increased on a number of lamina propria immune cells. Such immune activation contributes to the imbalance in Th1/Th2/Treg ratios. Soluble ST2 is released into the peripheral blood, which correlates with the markers of gut damage and of immune activation. B: During chronic HIV infection, epithelial gut damage extends with persistent IL-33 secretion and immune activation. IL-33 and TGF-β contribute to the tissue fibrosis. CD4 T-cells gradually decrease in the periphery and the plasma sST2 levels decline in comparison to the acute phase. Abbreviations: PAMPs = pathogen associated molecular patterns; DAMP = damage associated molecular pattern; MΦ = macrophage; DC = dendritic cell; ILC2 = group 2 innate lymphoid cells; IL-33 = interleukin-33; ST2 = suppressor of tumorigenicity2; NK = natural killer cell; Th1 = T helper cell type 1; Th2 = T helper cell type 2; Treg: regulatory T-cell.

intoxication, alcohol and viral hepatitis (Masubuchi et al., 2009). The IL-33/ST2 axis was shown to be upregulated in all of these cases of hepatic failure.

Furthermore, adenovirus-induced hepatitis in mice, which caused increased hepatic expression of IL-33 and of ST2, was associated with attenuated liver injury, with an increase in Tregs, and with a decrease in macrophage, DC, and NK cell tissue infiltration (Liang et al., 2013). The same group recently showed in a murine LCMV infection model that IL-33 deficiency resulted in a marked reduction in the number of IFN-γ + γδ T and NK cells, and in an increased number of Th17 + γδ T-cells, 16 h post-infection (Liang et al., 2015). These changes were reversed by treatment with recombinant IL-33, which induced DC proliferation and cytokine production.

Recent studies have explored the contribution of the IL-33/ST2 axis to the pathology caused by HBV and HCV (Lei et al., 2015, Liang et al., 2013, Wang et al., 2012a, Roth et al., 2010, Gao et al., 2015) (Table-1). Roth et al. first reported significantly elevated sST2 serum concentrations in patients with hepatic insufficiency due to various infectious and non-infectious causes (Roth et al., 2010). Significant sST2 upregulation was found in patients with acute liver failure or with acute-on-chronic liver failure, compared to patients with chronic hepatic failure (CHF) and to healthy controls. sST2 levels in CHF were also significantly higher than in controls. The investigators also reported correlations between IL-33, sST2 and alanine aminotransferase (ALT) serum levels in acute and in chronic liver failure. These results suggest that the IL-33/ST2 axis is a modulator of immune activation/inflammation in liver failure, and that this axis could be used to differentiate different disease stages.

Wang et al. reported higher IL-33 serum levels in patients with chronic HBV infections compared to healthy controls; these levels decreased in response to a 12-week treatment with the *anti*-viral adefovir dipivoxil (Wang et al., 2012a). Interestingly, serum sST2 levels remained elevated in the chronically infected HBV patients who did not respond to therapy, and these levels did not correlate with plasma IL-33 levels. These results suggest that sST2 is an early marker of acute liver failure, while elevation of IL-33 is linked to the development and to the progression of liver fibrosis. The same group also reported higher IL-33 levels in patients with chronic HCV infection compared to patients who spontaneously cleared infection or to healthy controls. They also showed that serum IL-33 levels correlated with serum aspartate transaminase (AST) levels in chronically infected HCV patients (Wang et al., 2012b). Furthermore, the IL-33 level decreased after 12 weeks of interferon treatment; this observation is consistent with the decreased levels of IL-33 observed in adefovir dipivoxil-treated patients with chronic HBV infection (Wang et al., 2012a). Finally, the elevated levels of sST2 observed in the studies of HCV and of HBV patients did not correlate with IL-33 levels, nor did the sST2 levels decrease with treatment. These findings suggest that IL-33 and ST2 contribute to the hepatic damage caused by HBV and HCV infections. Gut epithelial damage with microbial translocation also appears to play a role in inducing the hepatic damage that occurs in HBV and HCV infections.

Lei et al. showed higher sST2 levels with no difference in IL-33 levels, in HBV patients with acute-on-chronic liver failure, compared to controls and to patients with chronic HBV infection (Lei et al., 2015). These increased sST2 levels correlated with disease severity and predicted poor survival. At the cellular level, Marvie et al. showed an association between IL-33 and ST2 overexpression in the liver and in the development of hepatic fibrosis due to chronic infections with HBV or HCV, and due to alcoholic hepatitis (Marvie et al., 2010). This study also revealed that hepatic stellate cells and sinusoidal endothelial cells

are the main sources of IL-33 during the development of liver fibrosis in both mice and humans.

Collectively, these various lines of evidence suggest an important role for the IL-33/ST2 axis in the development of fibrosis in chronic infectious hepatitis. Large-scale prospective studies are required to assess the validity of the IL-33/ST2 axis as a predictor of disease progression, fibrosis and survival compared to other, currently used markers such as the AST-to-platelet ratio index, the fibrosis-4 (FIB-4) score, and more expensive, non-invasive tests, such as elastography and the FibroTest (Stasi and Milani, 2016).

4. The Contribution of the IL-33/ST2 Axis to Herpes Infections

IL-33 expression is induced in DCs, monocytes/macrophages and mast cells in response to inflammation (Arshad et al., 2016). Aoki et al. recently showed in a murine model that mast cell stimulation of herpes simplex virus 2 (HSV2)-infected keratinocytes induced increased IL-33 production (Aoki et al., 2013). They further showed that blocking ST2 on bone marrow-derived mast cells significantly inhibited their ability to produce TNF-α and IL-6. Interestingly, Oh et al. have shown in a murine model of mucosal HSV2 infection that the dysbiosis caused by oral antibiotic treatment directly impaired antiviral immune response, thus leading to defective immune protection (Oh et al., 2016). They also showed that after the depletion of commensal local microbiota, IL-33 secretion from vaginal epithelium inhibited effector T-cell migration to vaginal tissue and blocked the local production of IFN-γ. These findings indicate that antiviral defense mechanisms are regulated in part by IL-33 *via* microbial dysbiosis, which may be relevant for the development of HSV2 prophylactic strategies.

Cytomegalovirus (CMV), another member of herpesviradae family, causes latent infection in humans (Gianella et al., 2015). The signaling role of the IL-33/ST2 axis in the NK cell response during CMV infection in mice was reported by Nabekura et al. They showed in a murine model of MCMV infection that ST2-deficient Ly49H+ NK cells were impaired in their ability to drive MCMV-specific expansion of naïve cells into memory cells. Furthermore, when re-challenged with MCMV, IL-18R signaling was required for the secondary expansion of memory Ly49H+ NK cells. These findings suggest that IL-33 is released by damaged cells in the early phase of MCMV infection and that ST2 signaling transiently enhances MyD88 signaling to augment the proliferation of naive and memory Ly49H+ NK cells (Nabekura et al., 2015).

5. The Combined Effect of HIV and Co-infections on the IL-33/ST2 Axis

To date, studies assessing the effects of various viruses on the IL-33/ST2 axis have involved mono-infected animals or humans, as discussed above. It is expected that in the case of co-infections, viruses will synergize to enhance the IL-33 response. Studies involving co-infected animals and humans will be required to test this hypothesis.

6. The Therapeutic Potential of the IL-33/ST2 Axis

There have been increasing efforts to develop a vaccine and a cure for HIV infection (Routy et al., 2016). Knowing the critical role played by the T-cell response in host defense, these strategies mainly focus on inducing effective Th1 and cytotoxic CD8 T-cell responses, although strategies that induce beneficial antibody responses are also being investigated. The use of molecules acting as DAMPs, including IL-33, as vaccine adjuvants that enhance Th1 potency has gained considerable attention in recent years (Villarreal and Weiner, 2015, Villarreal et al., 2014, Villarreal et al., 2015a). Unlike other peptide-adjuvant conjugates that directly activate antigen presenting cells (APCs) through pattern recognition pathways, an IL-33-boosted vaccine was shown to activate NKT-cells *via* several mechanisms, resulting in an indirect enhancement of APC function in a murine model of allergic airway inflammation (Anderson et al., 2014).

A few animal studies have been conducted in which IL-33 was tested as an adjuvant in vaccines against various pathogens. An intranasal vaccine containing recombinant influenza virus hemagglutinin and IL-33 induced elevated, influenza-specific plasma IgG levels, mucosal influenza-specific IgA, and increased expression of both Th1 and Th2–related cytokines, all of which led to the protection of the challenged mice that received this vaccine; in contrast, control mice whose vaccines did not contain IL-33 adjuvant were not protected (Kayamuro et al., 2010). In a murine LCMV model, Villarreal et al. reported an increase in the magnitude and in the function of antigen-specific CD8 T-cells upon immunization with a DNA vaccine coadministered with IL-33 (Villarreal et al., 2015b). Antigenic re-stimulation led to the expansion of these polyfunctional cytotoxic cells *in vivo*, which conferred efficient protection against a lethal dose of LCMV. The IL-33 adjuvant also enhanced potent HIV-specific responses in a vaccine setting. Moreover, IL-33 co-administration led to increased numbers of effector CD8 T-cells compared to the administration of vaccine alone.

A few animal studies have also shown the benefits of IL-33 in different models of infection. For example, Bonilla et al. showed in a murine model of LCMV infection that the IL-33 released by necrotic cells enhanced the activation and the clonal expansion of ST2+ CD8+ T lymphocytes, resulting in a LCMV-specific cytotoxic response (Bonilla et al., 2012). Other investigators used recombinant IL-33 in a murine influenza model to reduce lung impairment (Monticelli et al., 2011), while in a murine coxsackie B virus model of experimental pancreatitis, IL-33 induced the production of IFN-γ and TNF-α by CD8+ T and by NK cells, resulting in viral clearance (Sesti-Costa et al., 2013).

We have shown that in early HIV infection, sST2 levels are elevated (Mehraj et al., 2016). These sST2 levels correlated with the CD8 T-cell count, with immune activation and with microbial translocation, suggesting that sST2 is a marker of gut damage and of disease progression. Interestingly, no such associations were observed in patients with chronic HIV infection. As the roles of IL-33 and ST2 in viral infections are phase-dependent, therapeutic strategies need to be rationally designed according to each phase. Therefore, blockade of sST2 should be of therapeutic value during the acute phase, while blockade of IL-33 should be considered for the chronic phase (Okragly et al., 2016) when fibrosis develops in lymphoid tissues or in the liver. Further studies of the regulation of the intracellular and cytoplasmic expression of IL-33 during tissue damage in the gut will be required in order to develop therapeutic interventions, with a focus on epithelial cells, ILC2 and other cells that express the ST2 receptor.

7. Future Directions

The mechanisms linking IL-33-mediated T-cell proliferation and/or survival to cytokine production will benefit from further *in vivo* studies. The interaction of IL-33 with other IL-1 family members, such as IL-18, needs to be thoroughly investigated to identify potential synergistic effects that may further contribute to an adjuvant effect. Follicular helper T-cells (Tfh cells) are an important subset of T-cells that are involved in the formation and in the maintenance of germinal centers of secondary lymphoid organs where B cells mature and produce antibodies (Kerfoot et al., 2011); it remains unknown whether ST2 is expressed on Tfh cells. The expression of ST2 on Tfh cells could have important implications for vaccination by potentially contributing to the maturation of the antibody response by neighboring B cells, a process that requires CD4 T cell help.

A better understanding of the regulation of the transcription factors currently known to control ST2 expression, such as T-bet, GATA-3 and STATs, and of CTL-regulating transcription factors, will also be critical for the design of novel immunotherapies that target the IL-33/ST2 axis. The identification of other sources of sST2 beyond ILC2s, Th2 and Tregs, which may explain the dynamics of the IL-33/ST2 axis in various conditions, will also be required.

8. Concluding Remarks

Data from animal models and from a limited but increasing number of human studies have shed considerable light on the involvement of the IL-33/ST2 axis in various inflammatory conditions and in the pathogenesis of diseases including acute and chronic viral infections. The protective and destructive functions of this axis may eventually allow for the development of axis-specific therapies that vary according to the type, phase and/or location of the infection. Translational studies involving blood and damaged tissues will be required to further elucidate the roles of the IL-33/ST2 axis in infection and in immunity so that novel immunotherapeutic approaches can be designed to reduce inflammation and to contribute to vaccine and cure strategies for the various diseases to which this axis contributes.

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References

Ahmad, R., Sindhu, S.T., Toma, E., Morisset, R., Ahmad, A., 2002. Elevated levels of circulating interleukin-18 in human immunodeficiency virus-infected individuals: role of peripheral blood mononuclear cells and implications for AIDS pathogenesis. J. Virol. 76, 12448–12456.

Alves-Filho, J.C., Sonego, F., Souto, F.O., Freitas, A., Verri JR., W.A., Auxiliadora-Martins, M., Basile-Filho, A., Mckenzie, A.N., Xu, D., Cunha, F.Q., Liew, F.Y., 2010. Interleukin-33 attenuates sepsis by enhancing neutrophil influx to the site of infection. Nat. Med. 16, 708–712.

Ananworanich, J., Chomont, N., Fletcher, J.L., Pinyakorn, S., Schuetz, A., Sereti, I., Rerknimitr, R., Dewar, R., Kroon, E., Vandergeeten, C., Trichavaroj, R., Chomchey, N., Chalermchai, T., Michael, N.L., Kim, J.H., Phanuphak, P., Phanuphak, N., 2015. Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification. J. Virus. Erad. 1, 116–122.

Anderson, R.J., Tang, C.W., Daniels, N.J., Compton, B.J., Hayman, C.M., Johnston, K.A., Knight, D.A., Gasser, O., Poyntz, H.C., Ferguson, P.M., Larsen, D.S., Ronchese, F., Painter, G.F., Hermans, I.F., 2014. A self-adjuvanting vaccine induces cytotoxic T lymphocytes that suppress allergy. Nat. Chem. Biol. 10, 943–949.

Andersson, C., Enserro, D., Sullivan, L., Wang, T.J., Januzzi, J.L., Benjamin, E.J., Vita, J.A., Hamburg, N.M., Larson, M.G., Mitchell, G.F., Vasan, R.S., 2016. Relations of circulating GDF-15, soluble ST2, and troponin-I concentrations with vascular function in the community: the Framingham Heart Study. Atherosclerosis 248, 245–251.

Aoki, R., Kawamura, T., Goshima, F., Ogawa, Y., Nakae, S., Nakao, A., Moriishi, K., Nishiyama, Y., Shimada, S., 2013. Mast cells play a key role in host defense against herpes simplex virus infection through TNF-alpha and IL-6 production. J. Invest. Dermatol. 133, 2170–2179.

Arshad, M.I., Khan, H.A., Noel, G., Piquet-Pellorce, C., Samson, M., 2016. Potential therapeutic aspects of alarmin cytokine interleukin 33 or its inhibitors in various diseases. Clin. Ther. 38, 1000–1016.

Barouch, D.H., Ghneim, K., Bosche, W.J., Li, Y., Berkemeier, B., Hull, M., Bhattacharyya, S., Cameron, M., Liu, J., Smith, K., Borducchi, E., Cabral, C., Peter, L., Brinkman, A., Shetty, M., Li, H., Gittens, C., Baker, C., Wagner, W., Lewis, M.G., Colantonio, A., Kang, H.J., Li, W., Lifson, J.D., Piatak Jr., M., Sekaly, R.P., 2016. Rapid inflammasome activation following mucosal SIV infection of rhesus monkeys. Cell 165, 656–667.

Baumann, C., Bonilla, W.V., Frohlich, A., Helmstetter, C., Peine, M., Hegazy, A.N., Pinschewer, D.D., Lohning, M., 2015. T-bet- and STAT4-dependent IL-33 receptor expression directly promotes antiviral Th1 cell responses. Proc. Natl. Acad. Sci. U. S. A. 112, 4056–4061.

Becerra, A., Warke, R.V., De Bosch, N., Rothman, A.L., Bosch, I., 2008. Elevated levels of soluble ST2 protein in dengue virus infected patients. Cytokine 41, 114–120.

Blom, L., Poulsen, L.K., 2012. IL-1 family members IL-18 and IL-33 upregulate the inflammatory potential of differentiated human Th1 and Th2 cultures. J. Immunol. 189, 4331–4337.

Bonilla, W.V., Frohlich, A., Senn, K., Kallert, S., Fernandez, M., Johnson, S., Kreutzfeldt, M., Hegazy, A.N., Schrick, C., Fallon, P.G., Klemenz, R., Nakae, S., Adler, H., Merkler, D., Lohning, M., Pinschewer, D.D., 2012. The alarmin interleukin-33 drives protective antiviral CD8(+) T cell responses. Science 335, 984–989.

Cao, W., Mehraj, V., Kaufmann, D.E., Li, T., Routy, J.P., 2016. Elevation and persistence of CD8 T-cells in HIV infection: the Achilles heel in the ART era. J. Int. AIDS Soc. 19, 20697.

Cayrol, C., Girard, J.P., 2009. The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1. Proc. Natl. Acad. Sci. U. S. A. 106, 9021–9026.

Cayrol, C., Girard, J.P., 2014. IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. Curr. Opin. Immunol. 31, 31–37.

Chen, L.Q., De Lemos, J.A., Das, S.R., Ayers, C.R., Rohatgi, A., 2013. Soluble ST2 is associated with all-cause and cardiovascular mortality in a population-based cohort: the Dallas Heart Study. Clin. Chem. 59, 536–546.

Fitch, K.V., Defilippi, C., Christenson, R., Srinivasa, S., Lee, H., Lo, J., Lu, M.T., Wong, K., Petrow, E., Sanchez, L., Looby, S.E., Hoffmann, U., Zanni, M., Grinspoon, S.K., 2016. Subclinical myocyte injury, fibrosis and strain in relationship to coronary plaque in asymptomatic HIV-infected individuals. AIDS.

Gao, S., Huan, S.L., Han, L.Y., Li, F., Ji, X.F., Li, X.Y., Fan, Y.C., Wang, K., 2015. Overexpression of serum sST2 is associated with poor prognosis in acute-on-chronic hepatitis B liver failure. Clin. Res. Hepatol. Gastroenterol. 39, 315–323.

Gao, Y., Liu, Y., Yang, M., Guo, X., Zhang, M., Li, H., Li, J., Zhao, J., 2016. IL-33 treatment attenuated diet-induced hepatic steatosis but aggravated hepatic fibrosis. Oncotarget.

Gianella, S., Massanella, M., Wertheim, J.O., Smith, D.M., 2015. The sordid affair between human herpesvirus and HIV. J. Infect. Dis. 212, 845–852.

Hayakawa, H., Hayakawa, M., Kume, A., Tominaga, S., 2007. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. J. Biol. Chem. 282, 26369–26380.

Hazlett, L.D., Mcclellan, S.A., Barrett, R.P., Huang, X., Zhang, Y., Wu, M., Van Rooijen, N., Szliter, E., 2010. IL-33 shifts macrophage polarization, promoting resistance against *Pseudomonas aeruginosa* keratitis. Invest. Ophthalmol. Vis. Sci. 51, 1524–1532.

Hunt, P.W., Sinclair, E., Rodriguez, B., Shive, C., Clagett, B., Funderburg, N., Robinson, J., Huang, Y., Epling, L., Martin, J.N., Deeks, S.G., Meinert, C.L., Van Natta, M.L., Jabs, D.A., Lederman, M.M., 2014. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. J. Infect. Dis. 210, 1228–1238.

Iannello, A., Samarani, S., Debbeche, O., Ahmad, R., Boulassel, M.R., Tremblay, C., Toma, E., Routy, J.P., Ahmad, A., 2009. Potential role of interleukin-18 in the immunopathogenesis of AIDS: involvement in fratricidal killing of NK cells. J. Virol. 83, 5999–6010.

Jenabian, M. A., El-Far, M., Vyboh, K., Kema, I., Costiniuk, C. T., Thomas, R., Baril, J. G., Leblanc, R., Kanagaratham, C., Radzioch, D., Allam, O., Ahmad, A., Lebouche, B., Tremblay, C., Ancuta, P., Routy, J. P., Montreal Primary, I. & Slow Progressor Study, G. 2015. Immunosuppressive tryptophan catabolism and gut mucosal dysfunction following early HIV infection. J. Infect. Dis., 212, 355–66.

Jones, L.A., Roberts, F., Nickdel, M.B., Brombacher, F., Mckenzie, A.N., Henriquez, F.L., Alexander, J., Roberts, C.W., 2010. IL-33 receptor (T1/ST2) signalling is necessary to prevent the development of encephalitis in mice infected with *Toxoplasma gondii*. Eur. J. Immunol. 40, 426–436.

Jovanovic, I.P., Pejnovic, N.N., Radosavljevic, G.D., Arsenijevic, N.N., Lukic, M.L., 2012. IL-33/ST2 axis in innate and acquired immunity to tumors. Oncoimmunology 1, 229–231.

Kakkar, R., Lee, R.T., 2008. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat. Rev. Drug Discov. 7, 827–840.

Kayamuro, H., Yoshioka, Y., Abe, Y., Arita, S., Katayama, K., Nomura, T., Yoshikawa, T., Kubota-Koketsu, R., Ikuta, K., Okamoto, S., Mori, Y., Kunisawa, J., Kiyono, H., Itoh, N., Nagano, K., Kamada, H., Tsutsumi, Y., Tsunoda, S., 2010. Interleukin-1 family cytokines as mucosal vaccine adjuvants for induction of protective immunity against influenza virus. J. Virol. 84, 12703–12712.

Kerfoot, S.M., Yaari, G., Patel, J.R., Johnson, K.L., Gonzalez, D.G., Kleinstein, S.H., Haberman, A.M., 2011. Germinal center B cell and T follicular helper cell development initiates in the interfollicular zone. Immunity 34, 947–960.

Latz, E., Xiao, T.S., Stutz, A., 2013. Activation and regulation of the inflammasomes. Nat. Rev. Immunol. 13, 397–411.

Lei, Z., Mo, Z., Zhu, J., Pang, X., Zheng, X., Wu, Z., Wang, K., Li, X., Xie, D., Gao, Z., 2015. Soluble ST2 plasma concentrations predict mortality in HBV-related acute-on-chronic liver failure. Mediat. Inflamm. 2015, 535938.

Li, D., Guabiraba, R., Besnard, A.G., Komai-Koma, M., Jabir, M.S., Zhang, L., Graham, G.J., Kurowska-Stolarska, M., Liew, F.Y., Mcsharry, C., Xu, D., 2014a. IL-33 promotes ST2-dependent lung fibrosis by the induction of alternatively activated macrophages and innate lymphoid cells in mice. J. Allergy Clin. Immunol. 134 (1422–1432), e11.

Li, P., Lin, W., Zheng, X., 2014b. IL-33 neutralization suppresses lupus disease in lupus-prone mice. Inflammation 37, 824–832.

Liang, Y., Jie, Z., Hou, L., Aguilar-Valenzuela, R., Vu, D., Soong, L., Sun, J., 2013. IL-33 induces nuocytes and modulates liver injury in viral hepatitis. J. Immunol. 190, 5666–5675.

Liang, Y., Jie, Z., Hou, L., Yi, P., Wang, W., Kwota, Z., Salvato, M., De Waal Malefyt, R., Soong, L., Sun, J., 2015. IL-33 promotes innate IFN-gamma production and modulates dendritic cell response in LCMV-induced hepatitis in mice. Eur. J. Immunol. 45, 3052–3063.

Lu, J., Kang, J., Zhang, C., Zhang, X., 2015. The role of IL-33/ST2L signals in the immune cells. Immunol. Lett. 164, 11–17.

Martin, N.T., Martin, M.U., 2016. Interleukin 33 is a guardian of barriers and a local alarmin. Nat. Immunol. 17, 122–131.

Marvie, P., Lisbonne, M., L'helgoualc'h, A., Rauch, M., Turlin, B., Preisser, L., Bourd-Boittin, K., Theret, N., Gascan, H., Piquet-Pellorce, C., Samson, M., 2010. Interleukin-33 overexpression is associated with liver fibrosis in mice and humans. J. Cell. Mol. Med. 14, 1726–1739.

Masubuchi, Y., Sugiyama, S., Horie, T., 2009. Th1/Th2 cytokine balance as a determinant of acetaminophen-induced liver injury. Chem. Biol. Interact. 179, 273–279.

Mehraj, V., Jenabian, M.A., Ponte, R., Lebouche, B., Costiniuk, C., Thomas, R., Baril, J.G., Leblanc, R., Cox, J., Tremblay, C., Routy, J.P., 2016. Montreal Primary HIV Infection, the Canadian Long-Term Non-Progressors Study Groups. The plasma levels of soluble ST2 as a marker of gutmucosal damage in early HIV infection. AIDS 30, 1617–1627.

Miller, A.M., 2011. Role of IL-33 in inflammation and disease. J. Inflamm. (Lond) 8, 22.

Miller, A.M., Xu, D., Asquith, D.L., Denby, L., Li, Y., Sattar, N., Baker, A.H., Mcinnes, I.B., Liew, F.Y., 2008. IL-33 reduces the development of atherosclerosis. J. Exp. Med. 205, 339–346.

Miyagaki, T., Sugaya, M., Yokobayashi, H., Kato, T., Ohmatsu, H., Fujita, H., Saeki, H., Kikuchi, Y., Tamaki, T., Sato, S., 2011. High levels of soluble ST2 and low levels of IL-33 in sera of patients with HIV infection. J. Invest. Dermatol. 131, 794–796.

Molofsky, A.B., Savage, A.K., Locksley, R.M., 2015a. Interleukin-33 in tissue homeostasis, injury, and inflammation. Immunity 42, 1005–1019.

Molofsky, A.B., Van Gool, F., Liang, H.E., Van Dyken, S.J., Nussbaum, J.C., Lee, J., Bluestone, J.A., Locksley, R.M., 2015b. Interleukin-33 and interferon-gamma counter-regulate group 2 innate lymphoid cell activation during immune perturbation. Immunity 43, 161–174.

Monticelli, L.A., Sonnenberg, G.F., Abt, M.C., Alenghat, T., Ziegler, C.G., Doering, T.A., Angelosanto, J.M., Laidlaw, B.J., Yang, C.Y., Sathaliyawala, T., Kubota, M., Turner, D., Diamond, J.M., Goldrath, A.W., Farber, D.L., Collman, R.G., Wherry, E.J., Artis, D., 2011. Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. Nat. Immunol. 12, 1045–1054.

Moussion, C., Ortega, N., Girard, J.P., 2008. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin'? PLoS One 3, e3331.

Nabekura, T., Girard, J.P., Lanier, L.L., 2015. IL-33 receptor ST2 amplifies the expansion of NK cells and enhances host defense during mouse cytomegalovirus infection. J. Immunol. 194, 5948–5952.

Nygaard, U., Vestergaard, C., Johansen, C., Deleuran, M., Hvid, M., 2016. Measuring serum concentrations of interleukin-33 in atopic dermatitis is associated with potential false positive results. Springerplus 5, 33.

Oh, J.E., Kim, B.C., Chang, D.H., Kwon, M., Lee, S.Y., Kang, D., Kim, J.Y., Hwang, I., Yu, J.W., Nakae, S., Lee, H.K., 2016. Dysbiosis-induced IL-33 contributes to impaired antiviral immunity in the genital mucosa. Proc. Natl. Acad. Sci. U. S. A. 113, E762–E771.

Okragly, A.J., Hamang, M.J., Pena, E.A., Baker, H.E., Bullock, H.A., Lucchesi, J., Martin, A.P., Ma, Y.L., Benschop, R.J., 2016. Elevated levels of interleukin (IL)-33 induce bone pathology but absence of IL-33 does not negatively impact normal bone homeostasis. Cytokine 79, 66–73.

Pastorelli, L., Garg, R.R., Hoang, S.B., Spina, L., Mattioli, B., Scarpa, M., Fiocchi, C., Vecchi, M., Pizarro, T.T., 2010. Epithelial-derived IL-33 and its receptor ST2 are dysregulated in ulcerative colitis and in experimental Th1/Th2 driven enteritis. Proc. Natl. Acad. Sci. U. S. A. 107, 8017–8022.

Peine, M., Marek, R.M., Lohning, M., 2016. IL-33 in T cell differentiation, function, and immune homeostasis. Trends Immunol. 37, 321–333.

Petrasek, J., Bala, S., Csak, T., Lippai, D., Kodys, K., Menashy, V., Barrieau, M., Min, S.Y., Kurt-Jones, E.A., Szabo, G., 2012. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. J. Clin. Invest. 122, 3476–3489.

Ponte, R., Mehraj, V., Ghali, P., Couedel-Courteille, A., Cheynier, R., Routy, J.P., 2016. Reversing gut damage in HIV infection: using non-human primate models to instruct clinical research. EBioMedicine 4, 40–49.

Reichenbach, D.K., Schwarze, V., Matta, B.M., Tkachev, V., Lieberknecht, E., Liu, Q., Koehn, B.H., Pfeifer, D., Taylor, P.A., Prinz, G., Dierbach, H., Stickel, N., Beck, Y., Warncke, M., Junt, T., Schmitt-Graeff, A., Nakae, S., Follo, M., Wertheimer, T., Schwab, L., Devlin, J., Watkins, S.C., Duyster, J., Ferrara, J.L., Turnquist, H.R., Zeiser, R., Blazar, B.R., 2015. The IL-33/ST2 axis augments effector T-cell responses during acute GVHD. Blood 125, 3183–3192.

Rostan, O., Arshad, M.I., Piquet-Pellorce, C., Robert-Gangneux, F., Gangneux, J.P., Samson, M., 2015. Crucial and diverse role of the interleukin-33/ST2 axis in infectious diseases. Infect. Immun. 83, 1738–1748.

Roth, G.A., Zimmermann, M., Lubsczyk, B.A., Pilz, J., Faybik, P., Hetz, H., Hacker, S., Mangold, A., Bacher, A., Krenn, C.G., Ankersmit, H.J., 2010. Up-regulation of interleukin 33 and soluble ST2 serum levels in liver failure. J. Surg. Res. 163, e79–e83.

Routy, J.P., Mehraj, V., Cao, W., 2016. HIV immunotherapy comes of age: implications for prevention, treatment and cure. Expert. Rev. Clin. Immunol. 12, 91–94.

Salter, B.M., Oliveria, J.P., Nusca, G., Smith, S.G., Tworek, D., Mitchell, P.D., Watson, R.M., Sehmi, R., Gauvreau, G.M., 2016. IL-25 and IL-33 induce type 2 inflammation in basophils from subjects with allergic asthma. Respir. Res. 17, 5.

Samarani, S., Allam, O., Sagala, P., Aldabah, Z., Jenabian, M.A., Mehraj, V., Tremblay, C., Routy, J.P., Amre, D., Ahmad, A., 2016. Imbalanced production of IL-18 and its antagonist in human diseases, and its implications for HIV-1 infection. Cytokine 82, 38–51.

Schacker, T.W., Reilly, C., Beilman, G.J., Taylor, J., Skarda, D., Krason, D., Larson, M., Haase, A.T., 2005. Amount of lymphatic tissue fibrosis in HIV infection predicts magnitude of HAART-associated change in peripheral CD4 cell count. AIDS 19, 2169–2171.

Schiering, C., Krausgruber, T., Chomka, A., Frohlich, A., Adelmann, K., Wohlfert, E.A., Pott, J., Griseri, T., Bollrath, J., Hegazy, A.N., Harrison, O.J., Owens, B.M., Lohning, M., Belkaid, Y., Fallon, P.G., Powrie, F., 2014. The alarmin IL-33 promotes regulatory T-cell function in the intestine. Nature 513, 564–568.

Schmitz, J., Owyang, A., Oldham, E., Song, Y., Murphy, E., Mcclanahan, T.K., Zurawski, G., Moshrefi, M., Qin, J., Li, X., Gorman, D.M., Bazan, J.F., Kastelein, R.A., 2005. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 23, 479–490.

Secemsky, E.A., Scherzer, R., Nitta, E., Wu, A.H., Lange, D.C., Deeks, S.G., Martin, J.N., Snider, J., Ganz, P., Hsue, P.Y., 2015. Novel Biomarkers of Cardiac Stress, Cardiovascular Dysfunction, and Outcomes in HIV-infected Individuals. JACC Heart Fail. 3 pp. 591–599.

Sesti-Costa, R., Silva, G.K., Proenca-Modena, J.L., Carlos, D., Silva, M.L., Alves-Filho, J.C., Arruda, E., Liew, F.Y., Silva, J.S., 2013. The IL-33/ST2 pathway controls coxsackievirus B5-induced experimental pancreatitis. J. Immunol. 191, 283–292.

Shang, J., Zhao, J., Wu, X., Xu, Y., Xie, J., 2015. Interleukin-33 promotes inflammatory cytokine production in chronic airway inflammation. Biochem. Cell Biol. 93, 359–366.

Smithgall, M.D., Comeau, M.R., Yoon, B.R., Kaufman, D., Armitage, R., Smith, D.E., 2008. IL-33 amplifies both Th1- and Th2-type responses through its activity on human basophils, allergen-reactive Th2 cells, iNKT and NK cells. Int. Immunol. 20, 1019–1030.

Stasi, C., Milani, S., 2016. Non-invasive assessment of liver fibrosis: between prediction/prevention of outcomes and cost-effectiveness. World J. Gastroenterol. 22, 1711–1720.

Sun, Y., Zhang, J.Y., Lv, S., Wang, H., Gong, M., Du, N., Liu, H., Zhang, N., Jing, J., Zhou, C., Zhang, F., Wang, Z., 2014. Interleukin-33 promotes disease progression in patients with primary biliary cirrhosis. Tohoku J. Exp. Med. 234, 255–261.

Tang, S., Huang, H., Hu, F., Zhou, W., Guo, J., Jiang, H., Mu, R., Li, Z., 2013. Increased IL-33 in synovial fluid and paired serum is associated with disease activity and autoantibodies in rheumatoid arthritis. Clin. Dev. Immunol. 2013, 985301.

Vander Lugt, M.T., Braun, T.M., Hanash, S., Ritz, J., Ho, V.T., Antin, J.H., Zhang, Q., Wong, C.H., Wang, H., Chin, A., Gomez, A., Harris, A.C., Levine, J.E., Choi, S.W., Couriel, D., Reddy, P., Ferrara, J.L., Paczesny, S., 2013. ST2 as a marker for risk of therapy-resistant graft-versus-host disease and death. N. Engl. J. Med. 369, 529–539.

Villarreal, D.O., Siefert, R.J., Weiner, D.B., 2015a. Alarmin IL-33 elicits potent TB-specific cell-mediated responses. Hum. Vaccin. Immunother. 11, 1954–1960.

Villarreal, D.O., Svoronos, N., Wise, M.C., Shedlock, D.J., Morrow, M.P., Conejo-Garcia, J.R., Weiner, D.B., 2015b. Molecular adjuvant IL-33 enhances the potency of a DNA vaccine in a lethal challenge model. Vaccine 33, 4313–4320.

Villarreal, D.O., Weiner, D.B., 2015. IL-33 isoforms: their future as vaccine adjuvants? Expert Rev. Vaccines 14, 489–492.

Villarreal, D.O., Wise, M.C., Walters, J.N., Reuschel, E.L., Choi, M.J., Obeng-Adjei, N., Yan, J., Morrow, M.P., Weiner, D.B., 2014. Alarmin IL-33 acts as an immunoadjuvant to enhance antigen-specific tumor immunity. Cancer Res. 74, 1789–1800.

Volarevic, V., Mitrovic, M., Milovanovic, M., Zelen, I., Nikolic, I., Mitrovic, S., Pejnovic, N., Arsenijevic, N., Lukic, M.L., 2012. Protective role of IL-33/ST2 axis in Con A-induced hepatitis. J. Hepatol. 56, 26–33.

WANG, J., CAI, Y., Ji, H., Feng, J., Ayana, D.A., Niu, J., Jiang, Y., 2012a. Serum IL-33 levels are associated with liver damage in patients with chronic hepatitis B. J. Interf. Cytokine Res. 32, 248–253.

Wang, J., Zhao, P., Guo, H., Sun, X., Jiang, Z., Xu, L., Feng, J., Niu, J., Jiang, Y., 2012b. Serum IL-33 levels are associated with liver damage in patients with chronic hepatitis C. Mediat. Inflamm. 2012, 819636.

Yndart, A., Kaushik, A., Agudelo, M., Raymond, A., Atluri, V.S., Saxena, S.K., Nair, M., 2015. Investigation of neuropathogenesis in HIV-1 clade B and C infection associated with IL-33 and ST2 regulation. ACS Chem. Neurosci. 6, 1600–1612.