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IL-33 and Thymic Stromal Lymphopoietin in mast cell functions

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ABSTRACT

Thymic Stromal Lymphopoietin (TSLP) and Interleukin 33 (IL-33) are two cytokines released by cells that are in proximity to our environment, e.g., keratinocytes of the skin and epithelial cells of the airways. Pathogens, allergens, chemicals and other agents induce the release of TSLP and IL-33, which are recognized by mast cells. TSLP and IL-33 affect several mast cell functions, including growth, survival and mediator release. These molecules do not directly induce exocytosis, but cause release of *de novo* synthesized lipid mediators and cytokines. TSLP and IL-33 are also implicated in inflammatory diseases where mast cells are known to be an important part of the pathogenesis, e.g., asthma and atopic dermatitis. In this chapter we describe and discuss the implications of TSLP and IL-33 on mast cell functions in health and disease.

1. Introduction

Cytokines released by cells at barrier surfaces, e.g., keratinocytes of the skin and epithelial cells in the airways, constitute an important part of our host defense to pathogens, but are also part of the pathogenesis of some of the most common diseases in the industrial world, e.g., allergy, asthma and atopic dermatitis. Two such cytokines that recently have attracted a lot of attention are Thymic Stromal Lymphopoietin (TSLP) and Interleukin 33 (IL-33). These cytokines are released from keratinocytes and airway epithelial cells, as well as other cell types, upon encounter with for example pathogens, allergens, irritants, chemicals and, at least for IL-33, during cell stress and cell injury. The release of IL-33 by the latter two factors is explained by the fact that IL-33, in contrast to TSLP, is pre-synthesized and located in the nucleus of structural cells, allowing its release upon trauma (Moussion et al., 2008). TSLP and IL-33 are critical cytokines linking responses at the interface between the environment and the body with local and systemic immune responses. Initially these responses were thought to be mainly of the Th2 type, but the reactions can most likely be much broader, including other cell types and cytokines than those traditionally associated with Th2 responses (Villarreal and Weiner, 2014).

Mast cells are endowed with properties that are of particular importance for its role in connecting the responses at the barrier surface, which induce release of TSLP and IL-33, with the initiation of an immune response. First, mast cells are distributed in almost every tissue and are particularly abundant close to the epidermis, epithelial cell layer and endothelial cells, locations where TSLP and IL-33 are released. Second, mast cells express high numbers of the IL-33 receptor ST2, and probably are among the most ST2 positive cells of the immune system (Motakis et al., 2014). The expression and regulation of receptors for TSLP on mast cells are less clear. Third, mast cells respond rapidly and release a variety of mediators that act both on the vasculature system and immune cells. This means that tissue responses to mast cell mediators are extensive. Furthermore, IL-33 and TSLP also affect other properties in mast cell biology, including growth, development, survival, attachment, which have important effects on the overall inflammatory response and probably are of particular importance for the pathology of different diseases where the IL-33/TSLP – mast cell link is implicated.

We have previously reviewed the role of mast cell recognition

Abbreviations: Bcl-XL, B-cell lymphoma-extra large; BMMCs, bone marrow-derived murine mast cell; ECM, extracellular matrix; eQTL, Expression Quantitative Trait Loci; GM-CSF, Granulocyte-macrophage colony-stimulating factor; Hck, hematopoietic cell kinase; IL-1RL1, IL-1 receptor-like 1; MCP-1, Monocyte chemoattractant protein-1; MDM2, Mouse double minute 2 homolog (MDM2) also known as E3 ubiquitin-protein ligase; MIP-2, Macrophage Inflammatory Proteins-2; MIP-1α, Macrophage Inflammatory Proteins (MIP) -1α; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; SCF, stem cell factor; SNP, Single Nucleotide Polymorphism; STAT, Signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha; TSLP, Thymic Stromal Lymphopoietin

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of IL-33 in the context of cell injury/trauma (Lunderius-Andersson et al., 2012) and allergy (Saluja et al., 2015). In this chapter we review the expression and release of TSLP and IL-33 and discuss their effect on mast cell functions and how this relates to diseases. There is strong clinical, as well as experimental evidence that IL-33 and TSLP are important upstream factors, released from e.g. epithelial cells, and acting on effector cells, that can perpetuate the inflammatory response in, e.g., allergic asthma (Cianferoni and Spergel, 2014; Makrinioti et al., 2014). A recent clinical trial demonstrated that an anti-TSLP monoclonal antibody attenuated eosinophilic inflammation and bronchoconstriction after allergen challenge (Gauvreau et al., 2014). This study provided the first direct compelling evidence that TSLP is a plausible target in human disease. Available data indicate that IL-33 might as well be a target for chronic inflammatory diseases and could have a role in the prevention of exacerbations. Further studies and better understanding of the function of the IL-33/TSLP – mast cell axis are needed to define their relative importance in the pathogenesis of, e.g., asthma and atopic dermatitis, and thereby develop new therapeutic interventions.

2. IL-33 and TSLP: cellular expression, release and regulation

2.1. Cellular expression

IL-33 is constitutively expressed in many different tissues and organs, particularly in epithelial cells from tissues exposed to the environment such as the airway, skin and intestinal epithelium (Moussion et al., 2008; Pichery et al., 2012). Fibroblastic reticular cells (FRCs) of lymphoid organs, smooth muscle cells and human endothelial cells in blood vessels also express high levels of IL-33 (Moussion et al., 2008; Pichery et al., 2012). Although IL-33 expression is constitutive in these tissues during homeostasis it can be further enhanced during inflammatory conditions. Increased expression of IL-33 in the nuclei of human airway epithelial cells has been observed in patients with asthma (Prefontaine et al., 2010) and chronic obstructive pulmonary disease (Byers et al., 2013). Moreover, IL-33 expression is inducible in immune cells such as macrophages (Chang et al., 2011), dendritic cells (Tjota et al., 2013) and mast cells (Hsu et al., 2010) during inflammation, although at much lower levels than in epithelial cells. Association of MCs and epithelial cytokine could be an important regulator in pathophysiological conditions especially in parasitic infection where MCs driven epithelial cytokines (IL-33, TSLP, IL-25) show protective role in protection against helminth infections (Hepworth et al., 2012).

Like IL-33, TSLP is an epithelium-derived cytokine most abundantly expressed by cells lining the barrier surfaces such as the lungs and skin and it is also highly expressed in thymic epithelial cells. Other cell types, including dendritic cells, mast cells, neutrophils, macrophages and basophils, as well as airway smooth muscle cells, have also been shown to produce TSLP (Kashyap et al., 2011; Redhu and Gounni, 2012). Constitutive TSLP release from intestinal epithelial cells may be involved in immune tolerance to commensal bacteria by conditioning mucosal dendritic cells (DCs) towards a non-inflammatory type (Rimoldi et al., 2005). Similarly, TSLP constitutively expressed in human thymic epithelial cells is responsible for the differentiation of Treg cells by modulating DC activity (Watanabe et al., 2005). Moreover, constitutive expression of TSLP has been found in human airway smooth muscle cells (Zhang et al., 2007). Even though constitutively expressed TSLP seems to be of importance in regulating homeostasis in some cases, TSLP production is mainly inducible during inflammatory conditions. TSLP mRNA levels have been found to be significantly increased in the airways of patients with asthma where epithelial cells, endothelial cells, neutrophils, macrophages and mast cells were significant sources of TSLP (Ying et al., 2008, 2005). In mast cells, the levels of TSLP mRNA were found to be enhanced by FcεRI cross-linking and were further augmented by IL-4 conditioning (Ying et al., 2005).

2.2. Release and regulation

IL-33 has been ascribed a dual function, acting as a cytokine upon release into the extracellular space where it can induce signal transduction in cells expressing the IL-33 receptor ST2/IL-1RAcP, or as a nuclear factor. In the absence of proinflammatory stimuli, IL-33 localizes to the nucleus by associating with chromatin (Carriere et al., 2007) and histones H2A–H2B *via* a short chromatin-binding motif and is suggested a role as a transcriptional repressor (Roussel et al., 2008). How IL-33 is released into the extracellular space from this nuclear localization is enigmatic as IL-33 lacks a specific signal peptide to enable it to be processed for secretion *via* the ER–Golgi pathway. Cellular necrosis can lead to the release of stored full-length biologically active IL-33 from the nuclear compartment in a passive process involving the disruption of the intracellular compartment, while processing by caspases during apoptosis results in IL-33 inactivation (Cayrol and Girard, 2009; Luthi et al., 2009). Because of this property, IL-33 has been ascribed the function of an endogenous danger signal with the task to alarm the immune system in the event of tissue damage (Enoksson et al., 2011; Lunderius-Andersson et al., 2012; Moussion et al., 2008). Pathogens, allergens and other environmental agents can trigger tissue damage which results in IL-33 secretion following necrotic cell death. Extracellular release of IL-33 can also be induced without any apparent cell death. In response to, e.g., *Alternaria* allergens, nuclear IL-33 has been shown to be released into the extracellular space from epithelial cells by a mechanism dependent on ATP-mediated activation of P2 purinergic receptors and sustained increases in intracellular calcium concentration (Kouzaki et al., 2011). In addition, IL-33 activity has been shown to be regulated after release into the extracellular space by several proteases. Processing of full-length human IL-33 by the neutrophil proteases cathepsin G and elastase released during inflammation has been found to lead to increased biological activity of IL-33 (Lefrancais et al., 2012). Similarly, IL-33 cleavage by murine mast cell chymase, mMCP-4, has been demonstrated but in these studies hypothesized to limit danger-induced inflammation (Roy et al., 2014; Waern et al., 2013). However, in another study it was shown that mast cell chymase and tryptase cleavage of human IL-33 instead results in the formation of several mature forms with potentiated activity on e.g., ILC-2 (Lefrancais et al., 2014).

Although regulation of TSLP expression has not yet been fully elucidated, both endogenous and exogenous factors seem to be involved. Allergen exposure, viral and bacterial infections, trauma, air pollutants as well as cytokines have been shown to induce TSLP expression in airway epithelial cells, skin cells and immune cells (Allakhverdi et al., 2007a). More specifically, TSLP has been shown to be induced by a TLR3 ligand (dsRNA) in primary human airway epithelial cells (Kato et al., 2007), by exposure to allergen-derived proteases including *Alternaria* through the involvement of PAR-2 in a human bronchial epithelial cell line (Kouzaki et al., 2009), by airway administration of house dust mite extract in mice in a manner dependent on TLR4 expression in airway structural cells (Hammad et al., 2009) and by exogenous IL-33 in epithelial cells from the gut (Humphreys et al., 2008). Exposure to proinflammatory cytokines, e.g., a combination of TNF-α and IL-1β has also been found to promote the release of TSLP in primary human small airway epithelial cells (Allakhverdi et al., 2007a).