Clinical Case Reports International

Short Communication
Published: 12 Mar, 2019

IL-33 and the Role of Genetics and Cytokines in Allergic Reactions

*Sibin Nair**

Department of Medicine, Saint James School of Medicine, USA

Short Communication

Cytokines and Genetics Involved in Allergies

Allergy was originally defined by Clemens Von Pirquet as "an altered capacity of the body to react to a foreign substance." Nowadays the definition is more refined to a "disease following a response by the immune system to an otherwise innocuous antigen." Allergy is a type of hypersensitivity reaction that involves the response through Immunoglobulin E (IgE) when bound to the high-affinity FC receptor on mast cells. With almost half of North American population having allergies to one or more common environmental antigens, it is imperative for us to look at the most upstream level involved in this reaction pathway. Though allergic reactions are rarely life-threatening it is a common issue in today's society that had led to much distress and loss of time.

To truly understand the mechanisms of an allergic reaction, we will try to analyze the earliest beginning of a reaction by looking at the impact of genetics and the cytokines involved in allergic reaction. While the most classical and common pathway involving IL-4 has been studied, we will be looking at a newer, less explored pathway involving IL-33 which has been very significant in allergic reactions and can be used as a future target for therapy.

IL-33 and ST-2

There are a group of damage-associated molecules released by tissue epithelial cells in response to external stimuli. These molecules are known as "alarmins." One of the main alarmins being studied has been Interleukin-33 (IL-33). Originating from the IL-1 family of cytokines, IL-33 has been recently observed to be expressed in many allergy responsive cells such as epidermal, smooth muscle and epithelial cells. As we analyze allergies and the human response, it is important to appreciate this on an upstream level to comprehend all the signaling pathways and use this to evolve our knowledge base to create better treatments in the future [1].

IL-33 plays a vital part in allergic response through various pathways and one of the initial stages involve binding to a membrane-bound receptor called Suppression of Tumorigenecity 2 (ST-2 receptor) and an (IL 1-R co-receptor) IL-1Receptor accessory protein via a heterodimeric receptor complex. This leads to activation of the primary signal MyD88 cascade pathway via homotypic protein-protein reactions. Other pathways involved include an increase in IL-5 cytokines that are IL-4 independent producing T-cells. Th2 cells, in general, respond via two pathways: the classic pathway involves IL-4, STAT (signal transducers and activators of transcription proteins) and GATA3 (DNA sequence "GATA" binding transcription factors) cascades while the non-classical pathway induces IL-5 production. This is polarized by IL-33 via the ST2 receptor and leads to a stronger allergic response.

The IL-5 cytokine also increases production of NF-kB (nuclear factor KB), MAPKs (Mitogen Activated Protein Kinases) and OVA (Egg protein ovalbumin) that increase inflammation and activation of tissue-resident cells with ST-2. The IL-33/ST2 complex also increases TH2-inducing cytokines like Th17 that leads to cell-mediated airway inflammation via Mast Cells (MC).

The MyD88 pathway

The MyD88 signal cascade involves the MyD88 adaptor protein to increase production of several other proteins and cytokines including IRA K4 (Interleukin-1 receptor associated kinase 4), TRAF6 (transcription factor 6), IL-13 and IL-6. Increased IL-5 and induce goblet cell hyperplasia in respiratory epithelial cells [2]. This in turn leads to heavier mucus production in respiratory epithelial cells and a stronger allergic response. These responses were highlighted by when they found administration of IL-33 failed to induce IL-5 and IL-13 secretion by MyD88 -/- T cells [3]. They also found that IL-33 induces NF-kB p65 and the MAPK p38, JNK ½ (c-Jun N-terminal

OPEN ACCESS

Correspondence:
Sibin Nair, Department of Medicine, Saint James School of Medicine, The Quarter, A-1 2640, Anguilla, USA, E-mail: sibinnair31@gmail.com

Received Date: *13 Feb 2019*
Accepted Date: *08 Mar 2019*
Published Date: *12 Mar 2019*

Citation:
Nair S. IL-33 and the Role of Genetics and Cytokines in Allergic Reactions. Clin Case Rep Int. 2019; 3: 1094.

Copyright *© 2019 Sibin Nair. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

kinases) and ERK ½ (extracellular signal-regulated kinases). Though IL-33 was reported to be integral to mast cells and allergic responses, the role of ST2 has been controversial for Ag-specific asthma. They concluded in that the IL-33/ST2 signaling is more involved in acute allergic response than chronic allergies.

The processing and release of IL-33

As part of the IL-1 family, IL-33 does not possess signal peptide to release the proteins via endoplasmic reticulum and the Golgi pathway. Hence, via external stimuli like allergens or injury, IL-33 is released by epithelial, endothelial, smooth cells and fibroblasts. The involvement of IL-33 in the development of allergic rhinitis induced by ragweed pollen challenge as IL-33 knock-out mice failed to induce ragweed pollen induced allergic reaction [4]. They found that Type 2 Innate Lymphoid Cells (ILC2) localized in mucosal tissues like lung and intestine, adipose tissue and lymphoid organs like spleen and lymphoid tissue were major targets of IL-33 due to their high expression of ST-2 receptors. These cells also produced high quantities of type 2 cytokines IL-5 and IL-13 which was previously discussed as part of the signal cascade involving IL-33/ST2/MyD88. The various functions played by IL-33 have resulted in theorizing IL-33 to be both a cytokine and an intracellular nuclear factor with transcriptional regulatory functions [4].

The Novel Alarmin

IL-33 is considered a "novel alarmin" due to its secretion upon necrosis or damage and released upon response to antigen. It is notably increased in expression in asthmatic patients *vs.* normal patients. It has been reported to induce airway bronchoconstriction through mast cell activation in murine models and found IL-33 protein in the lungs of mice with OVA/alum-induced airway inflammation [3]. This is due to the increased expression of tryptophan hydroxylase I by IL-33 that leads to serotonin synthesis and storage causing airway obstruction in asthma. It is also noted to be higher in patients with atopic dermatitis founded in epidermal keratinocytes. The high number of ILC2s in epidermal skin cells and lymph nodes release IL-5 leading to eosinophilic dermatitis. These are some of the many ways IL-33 is involved in various allergic reactions.

Future uses and novel therapy targeting IL-33

To create an effective future treatment, we have to appreciate the basic genetic component of IL-33 and understand the target region. IL-33 consists of an N-terminal helix-turned helix motif responsible for nuclear translocation and chromatin binding. It also has an IL-1 like C-terminal domain, which is cleaved by a caspase to form a mature 18kDa peptide from the original 30 kDa peptide. The deletion of the N-terminal domain containing the chromatin-binding motif has led to early lethality in mice by constitutive secretion of IL-33 in serum leading to multi-organ failure [5].

One of the endogenous mechanisms that was studied was the recently reported IL-22 cytokine that originated from the IL-10, expressing REG3y from lung epithelial cells in mice that suppress IL-33 expression and accumulation of ILC2s in the lung. Another idea is to sequester ILL-33 in the nucleus of IL-33 producing cells. The parasite *Heligmosomoides polygyrus* releases a product named *H. Polygyrus* Alarmin Release Inhibitor (HpARI) that binds to IL-33 via the N-terminus and tethers active IL-33 within necrotic cells [6]. Other approaches involve controlling the bioactivity of IL-33 as it can be rapidly inactivated by oxidation of four critical cysteine residues that result in extensive reconfiguration of the ST2 receptors.

All these novel therapy approaches require further testing and clinical trials but the fact remains that IL-33 is a key factor in allergic responses. Targeting the IL-33/ST2 pathway will be a critical component in the future treatment of allergic reactions and the more extensive our knowledge grows on the vital IL-33 genetic and secondary pathways, the better future therapy will be to treat and prevent patients with allergic reactions.

References

1. Janeway CA Jr, Travers P, Walport M. Allergy and Hypersensitivity. In: Immunobiology: The Immune System in Health and Disease. 5th edition. New York: Garland Science; 2001. Chapter 12.
2. Stolarski B, Kurowska-Stolarska M, Kewin P, Xu D, Liew FY. IL-33 Exacerbates Eosinophil-Mediated Airway Inflammation. J Immunol. 2010;185(6):3472-80.
3. Kurowska-Stolarska M, Kewin P, Murphy G, Russo RC, Stolarski B, Garcia CC, et al. IL-33 Induces Antigen-Specific IL-5+ T Cells and Promotes Allergic-Induced Airway Inflammation Independent of IL-4. J Immunol. 2008;181(7):4780-90.
4. Saluja R, Khan M, Church MK, Maurer M. The role of IL-33 and mast cells in allergy and inflammation. Clin Transl Allergy. 2015;5:33.
5. Takatori H, Makita S, Ito T, Matsuki A, Nakajima H. Regulatory Mechanisms of IL-33-ST2-Mediated Allergic Inflammation. Front Immunol. 2018;9:2004.
6. Osbourn M, Soares DC, Vacca F, Cohen ES, Scott IC, Gregory WF, et al. HpARI Protein Secreted by a Helminth Parasite Suppresses Interleukin-33. Immunity. 2017;47(4):739-751.e5.