

## Significance of IL-15 in asthma pathogenesis.

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Immune-based diseases that are rising in prevalence jeopardize the health of the western world from the last decade [1,2]. In developing world 358 million people globally had asthma, 1990 [3]. A chronic inflammatory pulmonary disorder responsible for over 397,100 deaths in 2015 [4]. Asthma is one of these immune based chronic, inflammatory lung diseases characterized by variable airway obstruction, hyper responsiveness and remodelling [5-7]. Experimental research in the asthma field has largely focused on analysis of the cellular and molecular events induced by allergen exposure in sensitized animals and humans [8-12]. These research studies have been identified elevated production of IgE, mucus hyper secretion, and eosinophilic inflammation, which lead to lung function abnormalities and airway fibrosis [13-17]. Lung function abnormalities develop in chronic asthma disease and other chronic inflammatory processes on subsequent exposure to environmental inhalants such as allergens, organic and inorganic dusts, or autoimmune disease and sarcoidosis [18-23]. Antigen presenting cells (APCs) interact with and activate T cell subsets and initiate a series of immunological responses to develop airway disease. The airway inflammatory response in asthma is characterized by induced expression of multiple genes encoding cytokines, chemokines, and adhesion molecules, which are associated with recruitment of eosinophil's and Th2 lymphocytes [24]. These elevated levels of chemokines and cytokines are thought to be central regulators of many of the hallmark features of airway pathology including inflammation and airway hyperactivity [25-27]. In addition to the characteristic Th2 and Th3 mediated inflammatory response found in the airway during acute asthma episodes, chronic asthma is characterized by structural changes that are termed airway remodelling [24-28]. Remodelling-associated changes in the airway include peribronchial fibrosis with increased deposition of collagen (types I, III, and V), smooth muscle hypertrophy/hyperplasia, and mucus secretion. Repeated cycles of inflammation and repair in the airway in chronic asthma are considered to be the driving force for airway remodelling. Therefore, a great need to continue with innovative fundamental studies to uncover new possibilities for the therapeutic interventions for airway hyperactivity/obstruction and fibrosis. Currently, anti-inflammatory corticosteroid inhalers and other medications are available to treat airway inflammation and obstruction. These treatments show a significant reduction in inflammation; but fail to restrict or reverse the progression of the bronchial airway obstruction and fibrosis.

IL-15 is important in linking innate and adaptive antiviral immune responses, promoting natural killer (NK),  $\gamma\delta$  T cells and memory CD8 T cell mediated anti-viral immune responses [29-31]. It is expressed by a large number of cell types

including NK cells, Number of T cells, intestinal epithelial cells, monocytes, macrophages, and dendritic cells (DC). A significantly increased IL-15 is detected in steroid-treated patients asthmatics compared to non-steroid treated asthmatics [32]. Importantly, muscle and serum IL-15 protein levels decline progressively with advanced age is reported in mice [33]. Additionally, age-related decline in expression of mRNA coding for the "sushi-only" isoform of sIL-15R $\alpha$  was also observed, which indicates reduced IL-15 secretion and stability with aging in mice. Furthermore, IL-15 polymorphism and IL-15 deficiency is reported in pediatric asthma pathogenesis [34,35]. Still, IL-15's role is yet not clearly understood in asthma pathogenesis. Based on these reports suggest that IL-15 deficiency may be critical in promoting asthma pathogenesis; therefore, our current study tested the hypothesis whether IL-15 overexpression protect asthma pathogenesis including airway hyper responsiveness, resistance and compliance [36]. We have found in our experimental model validated that indeed endogenous deficiency of IL-15 promotes baseline airway resistance, which is rescued in same endogenous IL-15 deficient mice following rIL-15 treatment. Further, we provide evidence that rIL-15 treatment in allergen induced asthma model diminishes allergen-induced airway obstruction and improves airway compliance down regulate pro-inflammatory cytokines and mucus producing goblet cell hyperplasia in the lung compared to the controls. Furthermore, we validated a rIL-15 pre-treatment finding that improves allergen induced airway obstruction, reduced proinflammatory cytokine and goblet cell hyperplasia using the asthmatic IL-15 overexpressed mice. We also show that human IL-15 agonist treatment to asthmatic mice down regulates most of the characteristic features that includes airway obstruction and compliance. This indicates that IL-15 agonist will be a possible novel future therapeutic strategy for non-steroidal treatment of asthmatics. Lastly, we provide mechanistic pathway operational in IL-15 induced protection of asthma pathogenesis indicates that STAT5 regulate IL-15 induced regulatory T cells induction and activation that induces the levels of IFN- $\gamma$  and regulatory T cell induced IL-10. We believe our approach will provide a novel therapeutic molecule to restrict or reverse the progression of airway hyperactivity and bronchial fibrosis in asthma.

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