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The Roles of Interleukin-17A/F and IL-36Ra in Obese Asthmatic Children

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Abstract

Childhood asthma and obesity are serious and chronic public health problems that require specific treatment. The prevalence of asthma in obese individuals is higher than that of non-obese individuals. Despite the belief that obesity is a major risk factor in the development of asthma, the mechanisms and effects associated with obesity are yet to be explained. It was considered that these two diseases are associated with excess adipose tissue that predisposes patients to inflammation and could contribute to the pathogenesis and severity of asthma. IL-17A and IL-17F are cytokines with pro-inflammatory properties, and high levels were observed in the serum of children with asthma and obesity. Also, IL-36 is a proinflammatory cytokine that acts as a mediator between the innate and adaptive immune systems to induce CXCL8 and IL-17 expressions. It could be suggested that these pro-inflammatory cytokines could play a role in the association between the two conditions. However, the activities of these cytokines are inhibited by anti-inflammatory cytokines such as IL-36Ra. The present review aims to explain the role of proinflammatory cytokines in adipose tissue and airway structure, as well as the association between the Th17 cytokines and the IL-36 cytokine family.

1. Introduction

The prevalence of childhood asthma is on the increase due to the global increase in obesity prevalence (Okubo et al., 2017). Obesity is a major asthma risk, and reducing body weight significantly reduces the risk of asthma in children (Lang et al., 2018). Furthermore, it was demonstrated that obese children have an increased risk of asthma, and it may double the asthma incidence. Although there

are several genetic, immunological, mechanical effects, and behavioral factors that could explain some of the association between asthma and obesity, the obvious mechanisms are still unknown (Di Genova, Penta, Biscarini, Di Cara, & Esposito, 2018). Asthma is described as a chronic inflammatory disease associated with airway hyperresponsiveness that leads to reversible recurrent episodes and widespread airway obstruction within the lung (Youssef, Elbehidy, Shokry, & Elbehidy, 2013). Obesity, similar to asthma, is a pro-inflammatory condition. In obese individuals, the increased adipose tissue causes overproduction of proinflammatory cytokines, adipokines, and chemokines, which may, in turn, lead to airway hyperresponsiveness(Youssef et al., 2013) . Numerous epidemiological studies reported that high body mass index (BMI) is related with asthma severity, unresponsiveness to corticosteroid therapy, and poor asthma control in individuals with asthma (Leija-Martínez et al., 2020). Obesity is characterized by a body mass index of greater than or equal to the 95th percentile in children based on age and gender (Lang et al., 2018), and morbid obesity is characterized by a body mass index of greater than or equal to the 99th percentile (O'Sullivan et al., 2021) and systemic low-grade inflammation (Rastogi, 2020). In response to excessive fat intake, adipose tissues undergo hypertrophy and hyperplasia due to excessive body fat (Leija-Martínez et al., 2020; Reilly, 2005)

The low-grade inflammation associated with obesity is induced by adipose tissue, which could secrete several components such as adipokines and cytokines. Thus, it was suggested that the association between obesity and asthma is likely mediated by immunological mechanisms (Peters, Dixon, & Forno, 2018); in obesity, the excessive fatty acid could stimulate adipose tissue-resident macrophage to produce various proinflammatory cytokines, including TNF-α, IL-6, IL-1β, IL-23, IL-12, IL-15, and chemokines that attract leukocytes such as IL-8, MIP-1α, and MIP-1β, and Rantes lead to adipose tissue dysfunction(Lumeng, Bodzin, & Saltiel, 2007) (Chehimi, Vidal, & Eljaafari, 2017). Furthermore, adipose tissue is infiltrated by neutrophils and secrete enzymes such as neutrophil elastase, myeloperoxidase, and other pro-inflammatory mediators that together amplify the recruitment of various immune cells including dendritic cells, eosinophils, mast cells, macrophages, and lymphocytes for inflammatory response (Mraz & Haluzik, 2014) . In adipose tissue, the type of macrophage polarization varies based on the degree of adiposity. Adipose tissue in non-obese individuals mainly includes adipocytes and type 2 macrophages (M2) known as alternative macrophages (Lumeng et al., 2007) that release anti-inflammatory cytokines, IL-10 and arginase-1(Leija-Martínez et al., 2020) . Unlike non-obese individuals, adipose tissue in obese individuals has a large type 1 macrophage (M1) count, known conventionally as activated macrophages that release chemokines and pro-inflammatory cytokines which promote differentiation to Th17 (Lumeng et al., 2007). Also, IL-36 cytokines are expressed by immune cells and serve as a mediator between innate and adaptive immune systems (Hayran, Allı, Yücel, Akdoğan, & Turhan, 2020). IL-36 cytokine expression is increased in serum samples of obese individuals, and positive correlations were reported between IL-36α, IL-36β, IL-36γ serum concentrations, and BMI (Hayran et

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al., 2020). IL-36 cytokines induce the activation and recruitment of neutrophils and Th17 cells during airway inflammation (Moermans et al., 2021). This is why obesity is considered a major risk factor and modifier in asthma in the present review, and we aimed to indicate the role of IL-17A, IL-17F, IL-36, and IL-36Ra in obesity and asthma.

2. Th17 Cell and Effector Cytokines

Th17 cells are a subclass of $CD4^{+}$T-helper cells that produce IL-17A, IL-17F, IL-21, IL-22, and other proinflammatory cytokines. The orphan γt (ROR-γt) associated with the retinoic acid receptor is the Th17 cell differentiation transcription factor, induced by IL-6, TGF-β through the activation of transcription signal transducer and activator (STAT3) (Kudo et al., 2012). Furthermore, IL-23 is important for the maintenance of Th17 cells but not in their differentiation (Stockinger & Veldhoen, 2007) 17]. IL-17A/ IL-17F plays a key role in the disposal of extracellular and fungal pathogens. However, it was reported that the IL-17 producing effector T cell pathogenicity is involved in various autoimmune and inflammatory disorders (Bettelli, Korn, Oukka, & Kuchroo, 2008; Chehimi et al., 2017). IL-17 triggers the local neutrophil recruitment via the induction of chemokines and cytokine production. Furthermore, IL-17 regulates granule-monocyte colony-stimulating factor (GM-CSF) generated by epithelial cells; and thus, promotes the extension of the neutrophils (Bettelli et al., 2008). IL-17 could upregulate the expression of epithelial cell chemokines such as CXCL1, CXCL2, and CXCL8. The CXCL8 is a strong chemoattractant of neutrophils and antimicrobial peptides such as b-defensin-2 and mucin (MUC5AC and MUC5B)(Eyerich, Dimartino, & Cavani, 2017). In addition to several cytokines released by Th17, adhesion molecules are associated with the maturation and activation of neutrophils by increasing neutrophil elastase (NE) and myeloperoxidase enzyme (MPO) activity (Chehimi et al., 2017). Th17 cells could fill the gap between innate and adaptive immunity. In addition, they also promote the accumulation of the other subclass of T helper cells to replace the infection in the late stages of inflammation (Bettelli et al., 2008).

IL-17A is the most effective among the effector pro-inflammatory cytokines of the cell cytokines primarily released from the Th17 cells, as well as the $CD^{+}8$Tcells, γδTcells, neutrophils, eosinophils, and monocytes. The effects of this cytokine could be induced by the release of proinflammatory cytokines such as IL-6, IL-1β, and GM-CSF (Newcomb & Peebles Jr, 2013; Ricciardolo et al., 2017) as well as the chemokines such as CXCL1, CXCL2, CXCL5, and CXCL8 (IL-8) (Kudo et al., 2012).

IL-17F is a proinflammatory cytokine secreted by Th17 cells and monocytes. This cytokine, similar to IL-17A, induces the production of IL-6 and chemokines such as CXCL1 (GROα), GCP-2, and CXCL-8 (IL-8), increasing the recruitment of neutrophils (Bettelli et al., 2008; Ricciardolo et al., 2017).

IL-21 is secreted by Th17 cells, natural killer cells and T follicular cells. Its function is to promote the differentiation of the Th17 cells (Bettelli et al., 2008).

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IL-22 is an IL-10 family cytokine. It is secreted from the Th1 cells, Th17 cells, Th22 cells, and natural killer cells. The IL-22 receptor is expressed by the airway smooth muscle and epithelial cells. IL-22 synergizes with the TNF-α to promote the induction of CXCL1 and CXCL5 expression in bronchial epithelial cells (Eyerich et al., 2017).

3. The Biological Effects of IL-36 Family Cytokines

IL-36 cytokines were recently classified as IL-1 superfamily members. The IL-36 cytokines include four cytokines that were previously called IL-1F8, IL-1F6, IL-1F5, and IL-1F9, and renamed as IL-36β, IL-36α, IL-36γ and IL-36Ra (Hayran et al., 2020). All IL-36 receptor (IL-36R) agonists include IL-36α, IL-36β, IL-36γ and bind to the IL-36R complex that includes IL-1R-related protein 2 (IL-1RL2) and IL-1 receptor accessory protein (IL-1RAcp) to generate inflammatory pathways through the activation of the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK). In contrast, the IL-36 receptor antagonist (IL-36Ra) inhibits pro-inflammatory signals by binding to IL-36R (Carrier et al., 2011; Hayran et al., 2020). IL-36 cytokines are expressed by several types of immune cells, including monocytes, dendritic cells, and lymphocytes. Furthermore, they are expressed by bronchial epithelial cells (Hayran et al., 2020). IL-36 cytokines increase the expression of proinflammatory chemokines and cytokines, including CCL1, CXCL1, TNF-α, IL-12, IL-23, IL-6, and GM-CST, and stimulate dendritic cells. In addition to maturating the dendritic cells by inducing the costimulatory molecules CD80, CD86, and MHC-II, they induce IL-6, IL-1β, TNF-α, and IL-23 cytokines that promote the differentiation of the Th17 cells. They also enhance the polarization of naive $CD^{+}4$T cells into Th1 cells (Vigne et al., 2011). Furthermore, IL-36γ could enhance leukocyte recruitment by activating endothelial cells and increases the expression of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) (Bridgewood et al., 2017). It was demonstrated that Th17 cytokines, including IL-17A and IL-22, directly promote increased IL-36 cytokine expression and proinflammatory cytokine production, leading to a positive feedback cycle between Th17 and IL-36 cytokines (Carrier et al., 2011) . In normal human airway fibroblasts, IL-36 could stimulate the production of high proinflammatory cytokine and chemokine levels, including IL-6, GM-CSF, G-CSF, IL-8, CCL2, and CXCL10. IL-36 cytokines could also amplify the neutrophilic inflammatory response in the airways. TLR3 stimulation induces IL-36α and IL-36γ expressions that lead to the recruitment of Th17 cells and activation of the fibroblast, augmenting the inflammatory response(Queen, Ediriweera, & Liu, 2019) . However, IL-36 cytokines are also included in the pathogenesis of various inflammatory diseases (Queen et al., 2019). The cellular source of IL-36 cytokines and their effects in the immune cells were presented in Table 1.

4. IL-17A and IL-17F in Obesity and Asthma Cases

One of the main proinflammatory cytokines involved in both asthma and obesity is IL-17. IL-17 is a proinflammatory cytokine that acts directly on epithelial and smooth muscle airway cells and induces airway hyperresponsiveness (Kudo et al., 2012).

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Table 1. An overview of the IL-36 cytokines

IL-36 isoform Pro- inflammatory cytokines	Cellular Source	Immunological functions of IL-36 cytokines
IL-36α IL-6β IL-36γ	**Epithelial Cells**	↑pro-inflammatory mediators (Cytokines, chemokines and antimicrobial peptide). include IL-17, TNF-α, IL-6 CXCL1, CXCL2, CXCL8(Li et al., 2021; Sun, Kusminski, & Scherer, 2011; Wang, Yi, & Liang, 2021). IL-17 directly induces IL-36 expression(Ding, Wang, Hong, Lu, & Liu, 2018).
	Dendritic Cells	↑pro-inflammatory mediators, TLR9 activation and IFN-γ production(Wang et al., 2021)
	T cells	Th1 and Th17 polarization. regulate the Th17expresion and enhance the function of Th17 (Ngo, Kuczma, Maxim, & Denning, 2021; Sun et al., 2011).
	Monocyte and macrophage	↑proinflammatory mediators. IL-36γ stimulates alveolar and interstitial macrophages to generate more IL-36(Koss et al., 2021).
	neutrophil	↑chemotaxis and promote neutrophil infiltration(Li et al., 2021).
Anti-inflammatory **IL-36Ra** **Anti-inflammatory**	**Epithelial cells, DC, Macrophages and T cells**	Suppresses the activation of IL-36 R signaling pathway(Sun et al., 2011)

The major physiological role of IL-17 is to induce the release of IL-6, IL-8, GM-CSF, G-CSF from the airway epithelial cells, fibroblasts, and smooth muscle cells in the lungs, and induce the recruitment of neutrophils. In the airways, it was demonstrated that IL-17 increased the release of CXC chemokines in human bronchial epithelial cells, leading to the specific recruitment of neutrophils (Lindén, 2006). Active neutrophils could release IL-8, a potent neutrophil chemoattractant that responds to the inflammatory stimuli in asthmatic airways (Lindén, 2001). Furthermore, activation of the neutrophils leads to the release of azurophilic granule proteins, including neutrophil elastase (NE) and myeloperoxidase enzyme (MPO). NE and MPO could be responsible for airway hypersecretion and hyperresponsiveness (Hoshino et al., 2000). Furthermore, IL-17 upregulates the expression of mucin gene (MUC5B/CA) in the airway epithelium and could be a marker of goblet cell hyperplasia and mucus hypersecretion in airway diseases (Chen et al., 2003). The response to steroid therapy is reduced in obese asthmatic patients when compared to non-obese asthmatic patients (Al Heialy et al., 2020). Steroid refractory therapy is an important clinical finding and a major characteristic of severe asthma. A study by Soheila et al. demonstrated that serum IL-17 concentration and mRNA expression were higher in

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children with severe asthma when compared to those with mild and moderate asthma. Other studies reported similar findings on the correlation between IL-17 concentration and asthma severity. For example, AL-Ramli et al. reported that the IL17A/F concentration, Th17 lymphocyte count, and genetic expression of IL-17mRNA were higher in the bronchial tissue biopsies of severe asthmatic patients when compared to mild and moderate asthmatic patients. Furthermore, in a murine study, Mathews et al. compared two C57BL/6J mouse groups, where the first group was fed a high-fat diet (HFD) and the second group was fed chow feed for 3 months. The study reported that the synthesis of IL-17A preceded airway hyperresponsiveness, and IL-17A concentration and IL-17 mRNA expression increased in mice with airway hyperresponsiveness and obesity (Al-Ramli et al., 2009). However, a limited number of studies investigated the role of IL-17F in obese asthmatic patients. One of these studies was conducted by Han et al. and for the first time reported the correlation between dietary intake patterns, IL-17F, and risk of asthma. The study demonstrated that the serum IL-17F concentrations were higher in obese and morbidly obese asthmatic children when compared to normal and overweight children, while IL-17A concentration was unaffected. The serum IL-17A and IL-17F concentrations were consistent with a previous study where a healthier diet has led to a decrease in IL-17F concentration (Han et al., 2015). Collectively, all the above-mentioned studies emphasized the significance of IL-17A and IL-17F in the correlation between obesity and asthma and could explain the underlying factors behind the possible association between obesity and unresponsiveness to steroid therapy.

5. The Role of IL-36 Cytokines and IL-36Ra in Asthma and Obesity

IL-36 agonists are pro-inflammatory cytokines that could play a role in the development of obesity and metabolic diseases, and increased IL-36 cytokine concentrations were reported in obese patients (Giannoudaki et al., 2019). A study by Van Asseldonk et al. demonstrated that IL-36α cytokine was expressed in adipose tissue, IL-36α likely had a proinflammatory impact on adipocyte differentiation and was primarily secreted by the macrophage type 2 (M2). Furthermore, the study reported that IL-36α induced proinflammatory cytokine expression in adipocytes (Van Asseldonk et al., 2010). Also, Ramadas et al. demonstrated that intratracheal administration of recombinant mouse IL-36γ led to increased airway hyperactivity, neutrophilic infiltration, and increased mucus secretion in a study on intratracheal administration in a house dust mite murine asthma model (Ramadas, Ewart, Medoff, & LeVine, 2011). Similarly, a study by Moermans et al. reported elevated concentrations of IL-36 in sputum, which was positively correlated with neutrophilic airway inflammation. In contrast, sputum IL-36 levels were negatively correlated with eosinophilic inflammation (Moermans et al., 2021) . Another recent study by Liu et al. reported lower IL-36Ra expression levels in peripheral blood mononuclear and sputum mononuclear cells in asthmatic children when compared to healthy children. Also, the same study reported on asthma severity that IL-36Ra level was lower in moderate asthma when compared to mild asthma; the in vitro study demonstrated that recombinant IL-36Ra inhibited the release of proinflammatory cytokines, including IL-1β, IL-6, IL-17, and stimulated TNF-α release by the LPs.

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In a murine asthma model, recombinant IL-36Ra injection led to improvements in airway inflammation by inhibiting the NF-κB-IL-36R pathway (Liu, Li, Zheng, Han, & Huang, 2020) Very few studies are available on the role of the IL-36 cytokine family in asthma and obesity, while no studies investigated the role of IL-36 family cytokines in obese asthmatic patients.

6. Conclusion

The evidence reported in the literature suggested that both Th17cell-producing IL-17 cytokines and IL-36 family cytokines were involved in the inflammatory response in obese asthmatic patients. Furthermore, IL-17 cytokines and IL-36 family cytokines were involved in the neutrophilic airway inflammation, which may explain resistance to steroid therapy common in obese asthmatic patients. Furthermore, the information in the present review could contribute to novel targeted therapeutic strategies.

Conflicts of interest

There are no relevant conflicts of interest to disclose.

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