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Interleukin 4 inhibition as a potential therapeutic in pemphigus

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ABSTRACT

Pemphigus is an autoimmune bullous skin disease that results from desmosomal protein desmoglein 3 and 1 loss in pemphigus vulgaris and foliaceus, respectively. It can be considered as a Th2-dominant disease over-expressed by Th2 cell cytokines. Interleukin (IL)-4 is a key cytokine which can exacerbate Th2 over-expression in addition to isotype switching to immunoglobin (Ig)G1 and IgG4 that are responsible for desmoglein loss. Elevation of IL-4 level has also been reported in various studies. Considering the important role of IL-4 in severe phase of pemphigus and lack of effective and safeness therapy for this potentially fatal disease, anti-IL-4 therapy was introduced as a potential curative for pemphigus disease. This study reviewed all studies about any roles of IL-4 that can directly and indirectly be played in the development of pemphigus and IL-4 inhibition with interferons and dupilumab therapy were introduced as a novel pemphigus treatment for patients who are in relapse phase of the disease. Dupilumab was also introduced as a possible treatment for patients with severe pemphigus. It can directly inhibit IL-4 by targeting IL-4 α-chain receptor. IL-4 inhibition can lead to the creation of Th1:Th2 balance by various pathways, discussed in this study.

1. Introduction

Naïve CD4+ cell can be differentiated into diverse T helper (Th) cells, including Th1, Th2, Th3, regulatory type 1 cells (Tr1), follicular helper T cells (Tfh), Th9, Th17, Th22, and Th25 [1–7]. All these T cells are responsible for the production of a number of certain cytokines that are able to directly affect immune response. Among the mentioned T cells, Th1 and Th2 are the two well-characterized subsets. This type of cells plays a substantial role in different autoimmune disease. They produce cytokines, which could mediate immune response. Interleukin (IL) 4 is an important cytokine that is secreted predominantly by activated Th2 cells. It has an anti-inflammatory effect and can suppress Th1 responses. Furthermore, it provides protective immunity against the intracellular pathogens [8]. It was proven that IL-4 can promote the differentiation of naïve CD4+ T cells into Th2 [9–13]. This differentiation results in a positive feedback loop toward a more IL-4 production by new developed Th2 cells. On the other hands, IL-4 is considered a key cytokine for Th2 differentiation [14]. It can also inhibit pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, interferon gamma (IFN-γ) and tumor necrosis factor (TNF)-α [1].

There is a balance between Th1 and Th2 cells in healthy condition. Dominance of one of these T cells will result in serious immune disorders. These disorders may be due to the lack of some cytokines, which may be inhibited by the dominant ones and dominancy of some other cytokines. Disturbance in the level of cytokines can lead to imbalance of immune system (including T cells and B cells). This phenomenon was observed in majority of the autoimmune diseases. Rheumatoid arthritis (RA), type 1 diabetes and multiple sclerosis (MS) are autoimmune and inflammatory diseases, which usually appear in Th1 over expression situation [15]. In contrast, Th2 over activation can be observed clearly in allergy, asthma, pemphigus vulgaris (PV) and pemphigus foliaceus (PF) [15]. Anti-cytokine therapy can be an alternative treatment, if cytokines that are responsible for imbalance of immune system can be recognized by the determination of cytokine's levels in patients, before and after therapy, and also in the control group. Various anti-cytokines drugs are successfully used and their usage in treatment of different diseases is extending rapidly by different anti-cytokines drugs, which are under development. Despite the introduction of the possible role of anti-IL-4 therapy in controlling PV patients by [16], this study focused on pathways that may be induced or inhibited by IL-4. In addition, IL-4 inhibition was discussed as an emerging therapeutic potential in patients with pemphigus.

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2. Pemphigus disease

Pemphigus is a type of autoimmune disease, which is a potentially fatal disease. It is also as a result of the autoantibodies that block desmoglein (Dsg) 1 and 3 function. Clinically, pemphigus is characterized by large, bullous and erosive defects that can appear on skin or mucous membranes [17]. It is a rare disease with a variety of prevalence in different regions [18–21]. PV and PF are the most common subsets of pemphigus. PV is more frequent than PF in USA and Europe. However, PF is more common in South Africa and certain countries, such as Finland [22,23]. Dsg3, which is a desmosomal adhesion protein, is recognized as an important autoantigen in PV [24]. Dsg3 proteins are rich compared to Dsg1 in mucous membranes. This can explain the initial appearance of blisters on mucous membranes in patients with PV. In contrast, Dsg1 has a relatively higher concentration on the skin [17]. Both Dsg1 and Dsg3 exist in mucous membranes and skin, but in different concentrations. In patients with both skin and mucosal lesions, the autoantibodies of both Dsg3 and Dsg1 are identified [25]. This type of disorder could also be categorized in PV group. If only Dsg1 autoantibody is identified, it could most times be categorized into PF, which is limited to the skin [25]. However, there are some evidences that indicate PV diagnosis, when Dsg1 autoantibody exists, in the absence of Dsg3 autoantibody [26]. After the appearance of lesions on the skin, there is nearly always simultaneous detection of immunoglobin (Ig)G autoantibodies to Dsg1 and Dsg3. Some reports have detected IgA with or without IgG in pemphigus patients [27,28]. IgG antibody can be divided into four subclasses, including IgG1, IgG2, IgG3 and IgG4. In several studies, IgG4 was introduced as IgG dominant subclass in pemphigus [29–31]. IgG1 was also introduced as second IgG subclass, which is dominant in PV and PF [29,30]. There are various studies, which demonstrated that Th2-dominant IgG (IgG4) is predominant in the active stage of PV, while during remission, majority of the antibodies are IgG1 [32,33]. However, it is not true for all the conditions. Dhandha et al. [34] analyzed IgG1 and IgG4 levels in 92 patients with PV. It was reported in their study that both IgG4 and IgG1 subtypes remain elevated in remittent patients compared to the controls.

T cells have an important role in this autoimmune diseases, since T cells are responsible for the inhibition and maturation of autoantibodies production [35]. Th2 cell's response plays a critical role in PV and PF [35]. Th2 activity was suggested to be associated with the severity of PV [36,37]. In a study, a significant association of Th2 activity with relapse phase of disease has been demonstrated when compared with the controls and remittent disease, whereas no considerable Th2 cells response have been reported in patients with remittent disease or controls. In addition, Th2 activity was revealed to correlate with anti-Dsg3 IgG significantly [37].

2.1. IL-4 and isotype switching

As previously informed, IgG was mainly responsible for cellular dissociation and pemphigus. IgG4 subtype was identified as the dominant subclass of IgG, especially in active stage of the disease. According to this result, it seems that any pathway that leads to IgG1 or igG4 isotype switching may contribute in deterioration of pemphigus disease. One of the well-recognized factors that could induce IgG4 is IL-10 [38–40]. It was demonstrated that IL-10 can cause igG4 isotype switching. IL-4 can also directly and indirectly play a substantial role in B cell isotype switching. This caused isotype switching to IgE, which promotes its role in asthma [41–43]. This cytokine also has the ability of leading to more Th2 differentiation, with more Th2 meaning more IL-10. Thus, it can cause IgG4 isotype switching indirectly in this way. It was suggested that IL-10 may enhance IgG4 production by potentiating IL-4-induced IgG4 switching [40].

In addition to IL-10, IL-4 could also cause isotype switching to IgG4 directly [44,45]. Ishizaka et al. [45] demonstrated that IL-4 can be considered as a switch factor for the direct production of IgG4 *in vitro*. However, IL-4 had no effect on IgG1, IgG2, and IgG3 synthesis. To address this issue, limiting dilution analyses of lipopolysaccharides (LPS)-stimulated B cells have been conducted and have shown that IL-4 increases the frequency of precursors that give rise to IgG1 [41,42].

2.2. IL-4 cytokine level in PV and PF patients

There are various studies that reported the elevation of Th2 cytokines in PV and PF patients. In Indian population, an elevation in IL-4 cytokine level was reported in PV and PF patients as compared to the controls. Cytokine level was measured by enzyme-linked immunosorbent assay (ELISA). IL-4 level in PV and PF was considerably higher compared to the healthy controls, and it did not show any significant difference between PV and PF patients [46]. Elevation of IL-4 was also reported in two other studies for PV and PF patients [47,48]. However, in another report, the level of IL-4 was measured in 10 patients with oral PV using ELISA in Egyptian patients. No significant difference between the levels of IL-4 was observed as compared to 10 controls [49].

Regarding to this issue, some studies reported the level of IL-4 before and after four weeks of treatment with azathioprine in PV. It was demonstrated that after treatment, IL-4 level decreased in both mild and server patients [50]. In contrast, Zeoti et al. [51] detected lower IL-4 in PF patients as compared to the controls. In addition to IL-4 level in serum, the presence of high level of IL-4 was also confirmed in perilesional skin biopsies [52].

2.3. IL-4 and its role in PV and PF

IL-4 is a key cytokine of Th2 cells that was discovered in 1982. The main source of IL-4 is Th2 cells. In addition to Th2 cells, it can be produced by basophils, eosinophil cells, mast cells and natural killer cells, which expressed as NK1.1 [53].

It has been identified that there are two major types of IL-4 receptors (IL-4R). The type 1 IL-4R is responsible for IL-4 signaling and expressed on T cells and type 2 IL-4R is not expressed on T cells. Both types of IL-4R are common in IL-4Rα. Type 1 consists of IL-4Rα chain and IL-4Rγc chain, which are also a receptor of IL-2, IL-4, IL-7, IL-9 and IL-15 [54–56]. IL-4 cross-links IL-4Rα results in Janus kinase (JAK)1 activation and IL-4Rγc results in JAK3 activation. Finally, these activations can cause translocation of STAT6 to the nucleus, where it promotes various IL-4 inducible genes [57].

IL-4 plays a serious role in PV and PF. It is one of the most important Th2 cytokines, which was reported to be dominant in PV and PF by several authors. With the secretion of IL-4, Th2 cells produce additional IL-4 in a positive feedback loop. Moreover, it can inhibit Th1, which can result in magnifying imbalance between Th1 and Th2 cells. Limited evidence also confirmed the potential role of IL-4 in isotype switching of activated B cells into IgG1 and IgG4, the predominant IgG subclasses in both PV and PF.

These IgG subclasses can be considered as the main anti-Dsg1 and anti-Dsg3. In the presence of these anti desmogleins, Dsg1 and Dsg3 were seriously damaged, resulting into blister on the skin and mucous membrane. IL-4 could also result in mast cells and eosinophil cell's activation [58]. After activation of these cells, IL-4 could be secreted from them resulting into a positive feedback loop for the production of IL-4. This loop can cause naïve T cells differentiation toward the Th2 cell and inhibition of differentiation Th1 cells. Naïve T cells should be activated by IL-2 before