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The possible role of interleukin-35 and its therapeutic potential in pemphigus

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ABSTRACT

Pemphigus is an autoimmune disease that causes blistering and is life-threatening if left untreated. Nowadays, finding a promising treatment for pemphigus remains a serious challenge. Various treatments are currently recommended to treat this disease, but they rarely lead to complete and durable remission. Regulatory cells appear to have a critical role in numerous autoimmune diseases, so it is possible that promotion of these cells may induce remission. This study presents a new approach to treating pemphigus that has not been discussed to date. This approach introduces interleukin (IL)-35 as a new treatment for pemphigus. This cytokine could induce two different types of regulatory cell, including IL-35-that produces induced regulatory T cells and IL-35^{+} regulatory B cells, which could suppress both effector T cells and effector B cells. It seems that IL-35 may act as an efficient therapeutic strategy for pemphigus. It probably limits progression of the disease and may even contribute to long-lasting remission. However, further study is required to evaluate the efficacy and safety of treating pemphigus with IL-35.

Contents

1. Introduction

Pemphigus is an autoimmune disease characterized by extensive flaccid blistering and mucocutaneous erosions. It is a rare disease, in

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which anti-desmoglein (Dsg)1 and 3 immunoglobulin (Ig)G antibodies cause loss of epidermal cell–cell adhesion and this can cause chronic, progressive blistering of the mucous membranes and skin. Pemphigus can be classified according to various subtypes but the two most common are pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

Conventional treatments for pemphigus usually involve a delayed response and serious side effects. Additionally, some patients with pemphigus may be resistant to conventional therapies [1]. This lack of response and side effects experienced by some patients has led to emergence of alternative and adjuvant therapies to treat pemphigus [1,2]. Recently, increasing evidence has shown that rituximab is effective in pemphigus [3]. It targets B cells, which results in significant improvement in patients with severe pemphigus. In addition to B cells, several studies have been done on manipulating T cells in order to limit responses of autoreactive T cells [4–6]. This could be achieved by changing levels of certain cytokines via inhibition or induction of certain cytokines or T cell surface molecules.

Interleukin (IL)-35 is an IL-12 family composed of a heterodimer of α and β chains, which are p35 and Epstein-Barr virus-induced gene 3 (EBI3) proteins, respectively. In contrast to the other IL-12 family cytokines (IL-12 and IL-23), which have proinflammatory function, IL-35 appears to have a strictly regulatory function [7]. IL-12 and IL-23 are produced by antigen presenting cells (APCs). However, regulatory cells are the major source of IL-35 [7]. Considering the high regulatory capacity of this cytokine, it could be employed to reduce effector T cell functions and populations. This could reduce the severity of pemphigus as well as several other autoimmune diseases. This study attempted to clarify the possibility of an immunosuppressive role and therapeutic benefits of the relatively new discovered cytokine IL-35, in pemphigus.

2. Pemphigus and immune responses

Several types of cell, especially T cells and B cells are involved in development and progression of pemphigus. In the majority of studies on immune response during pemphigus, elevated responses of proinflammatory cytokines and increased B cell responses were reported [8,9]. However, decreased or impaired function has been observed in regulatory cells of pemphigus patients [10–12]. It is generally accepted that pemphigus is a T helper (Th)2 dominant disease. The results of several studies imply elevation of Th2 cells in this disease [13,14]. In addition, a decrease in Th1 population was also observed. However, there is scarce evidence showing that Th1 cells exceeded Th2 cells in chronic active PV [15]. Th17 cell is currently the focus of research on different types of autoimmune disease, such as rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE) and it may be a T cell subset that is involved in pemphigus [16–18]. Indeed, several new reports provide evidence that the Th17 cell and its associated cytokines are critical in pemphigus [11,19]. In addition to Th1 cells, Th2 cells, and Th17 cells, some other types of Th cell have been identified but their roles in pemphigus have not been discussed to date.

Overall, elevated responses of effector T cells are a possible cause of pemphigus initiation. Thus, any cellular activity that leads to suppression of effector T cells could lead to disease remission. Regulatory T cells (Tregs) act in this way and are capable of impairment of effector T cell functions. Interestingly, numerous effector T cells-associated cytokines may lead to prevention of Tregs differentiation, dysfunction and even reprogramming of these cells [20–22].

B cells are the most important in pemphigus activity and are deeply influenced by T cell responses [23]. Previously, it was thought that only B cells could produce autoantibodies in pemphigus. However, other subsets of B cell were discovered that could suppress effector B cell responses. Subsequently, B cells have been introduced as new weapons against autoimmune diseases [24]. It was concluded that regulatory B cells (Bregs) have a negative effect on immune response regulation by producing regulatory cytokines as well as direct interaction with pathogenic T cells via cell-to-cell contact.

3. Effector T cells and regulatory T cells

Autoreactive T cells are thought to have a central role in the pathogenesis of pemphigus [13,14,25,26]. The role of Th1 cells and Th2 cells in pemphigus has been discussed in several studies. Th17 cells and associated cytokines also were known as critical to pemphigus. Conversely, the role of other effector Th cells, including Th9, Th22, and follicular helper T (Tfh) remains unclear in this disease. In contrast to effector T cells, different subsets of Tregs act to prevent, down regulate, or limit auto aggressive immune responses.

3.1. T helper 1 and T helper 2

Naïve $CD4^+$ T cells can be differentiated into Th1 and Th2 cells in the presence of IL-12 and IL-4, respectively. Additionally, several lines of evidence demonstrate that these generated Th cells suppress each other. Several studies have reported a decrease in Th1 population but Th subset has been identified with involvement in pemphigus. Veldman et al. [15] reported that the number of autoreactive Th1 cells exceeded those of Th2 cells in chronic active PV. Thus, this type of cell may contribute to chronic active pemphigus.

Many studies have reported elevated level of Th2 population and its associated cytokines during pemphigus [13,14,27]. Research has also reported a significant association between Th2 activity and the active disease [13]. Indeed, a significant elevation in Th2 response was observed at onset of the disease [13]. Th2-associated cytokines have various different roles in pemphigus. IL-4 causes employment of a positive feedback loop toward Th2 maturation. Additionally, this cytokine causes IgE, IgG1, and IgG4 isotype switching (reviewed in [4]). Considering the critical role of IL-4 on different types of cell, including T cells, B cells, mast cell, and eosinophils, inhibition was suggested for improving of severe pemphigus [4,28]. In addition to IL-4, IL-21 has a critical role in the progression of pemphigus via alteration of the different immune responses associated with the various immune cells, including T cells, B cells, mast cells, and natural killers [29]. Another important cytokine is IL-6, which contributes in differentiation of Th17 cells and generation of IL-21 producing $CD8^+$ T cells [30]. Furthermore, it could lead to dysfunction of natural Treg (nTreg) and convert them to effector T cells [31]. It is noteworthy that between the Th2-assoiated cytokines, IL-10 has a dual nature in pemphigus. Generally, it is known as a regulatory cytokine, which could induce type 1 regulatory T (Tr1) cell and B10 cells. However, there is evidence to show that it contributes to isotype switching to IgG4, which is the most important factor in pathogenesis of pemphigus [32,33].

3.2. T helper 17

Th17 cells are a unique pro-inflammatory lineage of effector/memory Th cells, quickly identified as essential for promotion of several autoimmune diseases. This type of cell could secrete IL-17 as well as IL-17F, IL-21, and IL-22. Although TGF-β alone leads to differentiation of forkhead box *P*3 $(Foxp3)^+$ Tregs, Th17 cells can be generated from differentiation of naïve T cells in mice with a presence of TGF-β and IL-6 [34,35]. Moreover, the presence of IL-6 may result in a shift from a regulatory phenotype toward a Th17 [36]. Interestingly, IL-21, the cytokine produced by Th17 cell cooperates with TGF-β induced differentiation of the mouse Th17 cell, even in an absence of IL-6 [37]. In issue concerning development of Th17 cells from human $CD4^+$ T cells, is that it has been noticed that TGF-β and IL-21 uniquely promote this differentiation [38]. IL-21 secreted from individual naive CD4 + T cells acts in an autocrine manner to induce Th17 differentiation. IL-23 is another cytokine involved in the development of Th17 cells, which promotes cell expansion [39].

Despite the clear role of Th17 and its associated cytokines in inflammation and autoimmunity, its precise role in pemphigus is still uncertain. However, there is growing evidence to show an important role