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Review

Interleukin 21 as a new possible player in pemphigus: Is it a suitable target?

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ABSTRACT

Pemphigus is a rare autoimmune disease, which could be fatal without treatment. Recently, target therapy is increasingly being used in different autoimmune diseases. However, there are limited studies associated with target therapy in pemphigus. In this study, it was tried to identify the role of interleukin (IL) -21 in patients with pemphigus. Based on the available studies on the role of IL-21 associated with several cells, including T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells as well as regulatory B cells and regulatory T cells, the possible roles of this cytokine in pemphigus were discussed in detail. It was found that IL-21 is a crucial cytokine associated with pemphigus disease, which has not been discussed in this disease yet. It is able to promote T helper (Th) 2, Th17, T follicular helper (Tfh), CD8 + cytotoxic T lymphocytes (CTLs), NK and NKT cells. It also causes the production of immunoglobulin (Ig)G in addition to the decrease of Tregs. All the mentioned alterations seem to be involved in disease progression via different signaling pathways. Inhibition of these changes must cause improvement of disease severity. By inhibition of IL-21 or its receptor, it is expected that patients with severe pemphigus experience relative and gradual improvement. This inhibition could be induced by tofacitinib, which was approved by the US Food and Drug Administration as a treatment for rheumatoid arthritis patients, or anti-IL-21 monoclonal antibody, NNC114-0006. However, more studies are needed to confirm it as a promising therapy.

Contents

1. Introduction

Interleukin (IL)-21 is considered as a member of type 1 cytokine family, which was discovered in 2000 [1]. It is mainly produced by natural killer T (NKT) cells, T follicular helper (Tfh) cells as well as T helper (Th) 17 cells. This cytokine signals via heterodimers of the IL-21 receptor (IL-21R) [1,2] and the common cytokine receptor γ-chain (γ_c) [3]. IL-21 is one of the family members of γ_c cytokines, including IL-2, IL-4, IL-7, IL-9 and IL-15. The role of IL-21 has been studied in several diseases, including autoimmune diseases and different types of cancers [4,5]. It was identified as a factor that could accelerate disease progression. Thus, inhibition of this cytokine was recommended in multiple studies in order to control autoimmune disease severity [5–7]. In contrast, Holmdahl demonstrated that IL-21 and/or IL-21R play no role in development of autoimmune inflammatory disease as well as Th17-dependent disease [8].

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Pemphigus is a rare autoimmune disease, which could be considered as a life- threatening disorder. In this disease, immunoglobulin (Ig)G acts against the cell adhesion molecules. This will result in destroying desmoglein (Dsg)1 and Dsg3 that lead to development of lesions on skin or mucous membrane. The exact reason of this occurrence is not clearly identified, while the role of some cells and their productions are well understood in pemphigus [9]. For example, B cells act toward initiation and progression of this disease. There is a scientific consensus that these cells cause deterioration of pemphigus via secretion of autoantibodies against Dsg1 and Dsg3 proteins, which led to the emergence of new therapeutic options; associated with targeting B cells. Rituximab, which causes a decrease in B cell population, is increasingly being used to treating pemphigus disease [10]. Recently, Ahmed and Shetty [10] concluded that rituximab is the best biological agent, currently available for treatment of recalcitrant pemphigus. There are also some studies related to T cells and their productions in pemphigus disease [11–13]. However, the exact roles of several cytokines, which are predominantly produced by T cells, are not clear in this complex disorder. IL-21 is one of the most suspicious cytokines in autoimmune diseases that its role is increasingly discussed in these types of diseases [14–16]. Unfortunately, the role of IL-21 in pemphigus has not been discussed yet. In this study, the possible roles of IL-21 in pemphigus disease were discussed.

2. Effect of IL-21 on T cells, B cells and myeloid cells

2.1. T cells

Results of different studies implied the critical role of IL-21 in naïve T cell differentiation. It was demonstrated that IL-21 causes inhibition of Th1 cell differentiation. This leads to decreasing interferon gamma (IFN-γ) production significantly. This will occur through the repression of eomesodermin expression [17,18]. T-bet transcription factor, the main factor of Th1 development could inhibit GATA3, which is the master transcription factor of Th2 cells, via increase restrictive histone modifications to repression of Gata3 expression [19]. However, Strengell et al. [20] reported up-regulation of gene expression associated with innate immunity and Th1 response by IL-21. On that study, the induction of IFN-γ, T-bet, IL-12Rβ2, and IL-18R gene expression in natural killer (NK) cells, along with signal transducer and activator of transcription (STAT)3 activation was observed. These results suggest that IL-21 may have a possible role in Th1 cell responses. Regarding the suppression of Th1 cell differentiation by IL-21, it is expected that the number of Th2 cells increases rapidly. Fröhlich et al. [21] showed that IL-21 plays a crucial role in supporting polarized Th2 responses in vivo using IL-21Rα-deficient mice. However, it appeared to be superfluous for Th1 and Th17 responses. Despite the results implying the lack of IL-21 effect in Th17 cell response [21,22], various studies confirmed the critical role of IL-21 in Th17 cell differentiation [23–25]. IL-21 is considered as one of the Th17 cell productions, which could establish a positive feedback loop toward the Th17 promotion. Nurieva et al. [25] concluded that IL-21 is an autocrine cytokine that is sufficient and necessary for Th17 differentiation. It is worth mentioning that Th17 is possibly responsible for inflammatory diseases. Additionally, different studies confirmed its major role in pemphigus disease, which made it an attractive target [26,27]. In addition to IL-21, other cytokines such as transforming growth factor beta (TGF-β), IL-6 and IL-23 contributed in Th17 development, which is dependent on STAT3 and RORγt [28–31]. TGF-β plus IL-6 or IL-21 is known as the differentiation factors of Th17 cells. In addition, IL-23 acts as the growth and stabilization factor in the Th17 cells [32]. There are also some limited evidence that TGF-β is capable of reprogramming Th1 cells to Th17 cells [33].

IL-21 plays another role associated with CD4 + T cell differentiation. In several studies, it was demonstrated that IL-21 is able to suppress upregulation of forkhead box *P*3 (Foxp3), a master regulator of regulatory T cells (Tregs) in naïve Th cells [25,34,35]. In one of these studies, more than 150-fold decrease in Foxp3 + cells by IL-21 treatment and 200-fold increase in antigen-specific cytotoxic T lymphocytes (CTLs) were observed [35]. Several other studies reported that IL-21 acted in favor of CTL induction [36–38]. Zeng et al. [38] introduced IL-21 as a potent regulator of CD8 + T cell expansion and effector function, primarily in a synergistic context with IL-15. It was demonstrated that human naïve CD8 + T cells in the presence of IL-27 lead to an increase in IL-21 [39]. This will be considered as a positive feedback loop of IL-21 production, when IL-27 is present. Tfh cells, the main source of IL-21, are also affected in the presence of IL-21. In other words, this cytokine can induce Tfh cell differentiation. Thus, IL-21 may be an autocrine cytokine for Tfh differentiation. This manner was confirmed by Vogelzang and King [40] in 2007. Their results on IL-21 and IL-21R deficient mice revealed that IL-21 was an autocrine growth factor for Tfh cells.

2.2. B cells

Various studies on both of human and mouse confirmed that in addition to T cells, B cells could be influenced by IL-21. Despite this fact, IL-21 is not essential for B cell development. It was demonstrated that mice deficient in the receptor for IL-21 have normal lymphoid development [41]. However, it was shown that this cytokine is involved in plasma cell differentiation from both naïve and memory B cells [42]. IL-21 can affect B cells in other ways, depending on absence or presence of different signaling contexts, including B cell receptor (BCR), toll-like receptor (TLR) or T cell interaction. Effects of IL-21 on B cells are relatively complex issue, which were studied by several authors in this century. The roles of IL-21 in co-stimulation of human B cell proliferation that were induced by anti-CD40 were reported. However, suppression of proliferation stimulated by anti-IgM and IL-4 was another achievement associated with this point. These occurrences were confirmed in both mouse and human [2,41,43]. However, Mehta et al. [44] reported different results in a murine model. It was found that IL-21 does not enhance anti-CD40 induced proliferation of primary murine B cells, but does suppress the proliferation induced by anti-IgM and IL-4. It was indicated that in addition to inducting death of resting B cells in mice, IL-21 enhance Ig production, isotype switching and plasma cell production [43]. The apoptosis of resting primary murine B cells was also reported by other authors [44].

To investigate the effect of IL-21 on the fate of B cells, a comprehensive study was conducted in vitro, using two mouse strains [45]. For B cells stimulated through TLR4 and -9 proliferative responses were suppressed, and cell death was increased by IL-21, while a rise in the fraction of cycling cells and proliferative responses was observed by IL-21 for anti-CD40-stimulated B cells. As an overall conclusion related to regulation of B cells by IL-4, it was found that magnitude of IL-21-dependent apoptosis or co-stimulation is relevant to the mouse strain from which the B cells were derived in addition to the nature of the activating signals. Ettinger et al. [46] indicated that IL-21 is able to induce class switch recombination (CSR) and stimulate poorly responsive naïve cord blood B cells into IgG-secreting plasma cells in addition to its capability of plasma cell differentiation induction from CD27 + memory B cells.

IL-21 plays a critical role in changing the level of different antibodies that are produced by B cells. In respect to IgE and IgG antibodies, which are the most important ones during pemphigus, multiple studies were carried out. An analysis to find the role of IL-21 on IgE production and IL-4-induced IgE production from B cells and antigen-induced Th2 cell differentiation on mouse was carried out [47]. It was revealed that IL-21 did not affect Th2 cell differentiation, while it down-regulates IgE production from IL-4-stimulated B cells. In another study, higher production of the IgE in the mice deficient in the receptor for IL-21 compared to the wild-type was observed [41]. In contrast, surprisingly, Avery et al. [48] introduced IL-21 as an inducer of IgE production by CD40L-stimulated human naïve B cells. In respect to the role of IL-21 in IgE production, another study reported that IL-21 reduced IL-4-driven IgE synthesis by mitogen-stimulated human peripheral blood