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The dual nature of Interleukin-10 in pemphigus vulgaris

Michael Jeffrey Cho, **Christoph T. Ellebrecht**, and **Aimee S. Payne**

Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA

Abstract

The immunomodulatory cytokine interleukin-10 (IL-10) plays beneficial but also potentially detrimental roles in inflammation, infection, and autoimmunity. Recent studies suggest a regulatory role for IL-10-expressing B cells in the autoimmune blistering disease pemphigus vulgaris. Here we review the studies on IL-10 in pemphigus vulgaris and discuss the potential pathophysiological significance of these findings in comparison to prior studies of IL-10 in other human conditions. A better understanding of the complex roles of IL-10 in immune regulation may improve our understanding of pemphigus pathogenesis and treatment.

1. IL-10 regulation of host immune responses

IL-10 is an immunoregulatory cytokine whose primary function is to limit inflammatory responses. Its chief role as a negative immune regulator is evidenced in IL-10$^{-/-}$ mice, which develop severe intestinal inflammation due to the inability to control immune responses to gut-resident bacterial flora [1, 2]. Similarly, humans with mutations in IL-10 or its receptor develop early-onset enterocolitis [3, 4]. IL-10's myriad functions have previously been reviewed [5, 6]; its anti-inflammatory effects include inhibiting the production of pro-inflammatory cytokines such as IL-1, tumor necrosis factor alpha, and IL-12 from T cells and antigen presenting cells [7-9], inhibiting production of chemokines, downregulating expression of major histocompatibility (MHC) class II and co-stimulatory molecules such as CD86 to inhibit antigen presentation and induce tolerance [10-13], regulating immunoglobulin class switch in B cells (particularly to the IgG4 subclass) [14], and attenuating CD4^{+} T cell responses (**Figure 1**). Despite these predominantly negative immune regulatory functions, IL-10 can also stimulate immune responses by promoting the proliferation and cytotoxic activity of CD8+ T cells and natural killer cells [15-18], as well as the survival and antibody secretion of B cells [19, 20]. These effects are context-dependent, since inhibitory or pro-apoptotic effects of IL-10 on CD8^{+} T cells or B cells can also be observed under different experimental conditions [21, 22]. For example, IL-10 has been shown to promote apoptosis of B cells when added within 3 days of activation, whereas addition of IL-10 greater than 3 days after B cell activation supports their differentiation into antibody-secreting cells [22].

Correspondence should be addressed to A.S.P. (paynea@mail.med.upenn.edu).

IL-10's beneficial and detrimental roles in host immune responses are perhaps most apparent during infection, as IL-$10^{-/-}$ mice demonstrate enhanced clearance of bacterial, fungal, and viral infections (reviewed in [23, 24]), but at the expense of an amplified immune response that may potentially lead to septic shock [25]. Similarly, humans with IL-10 gene polymorphisms demonstrate altered susceptibility to a variety of viral and bacterial pathogens [23, 24], consistent with their genotype-phenotype predictions. Although caution is warranted in using mouse models to understand human inflammatory conditions, IL-10 signaling pathway gene expression profiles have been reported to demonstrate the highest Pearson correlations between mouse and human models, with similar changes in expression observed for 67-79% of pathway genes [26]. Thus, there appears to be reasonable conservation of IL-10 responses among mice and humans.

IL-10 can be produced by monocytes and macrophages, T and B lymphocytes, dendritic cells, other leukocytes (including mast cells, neutrophils, and eosinophils) and some epithelial cells, including keratinocytes [27-29]. IL-10 production by $CD4^+$ T cells is essential for immune homeostasis, since $CD4^+$ T cell-restricted deficiency of IL-10 causes intestinal inflammation in mice similar to the colitis observed in mice globally deficient in IL-10 [30]. In T cells, IL-10 expression defines a subset of T regulatory cells (Tregs) that can develop from either $CD4^+CD25^+FoxP3^+$ or $CD4^+CD25^+FoxP3^-$ precursors [31]. Within the B cell lineage, IL-10-producing subsets are not as restricted. Naïve $CD24^{hi}C38^{hi}$ transitional cells [32], $CD24^{hi}CD27^+$ memory cells [33], $CD73^-CD25^+CD71^+$ $IgG4^+$ cells [34], tissue-resident marginal zone cells [35], and plasma cells [36, 37] have all been reported to express IL-10. The expression of IL-10 defines a class of B cells with regulatory functions, also known as Bregs or B10 cells [38]. However, a defining transcriptional program that is necessary and sufficient to maintain Breg functions, analogous to FoxP3 in Tregs, has not been identified. IL-10 induces the expression of plasma cell transcription factors *Irf4*, *Xbp1*, and *Blimp1*, with a concomitant decrease in earlier B lineage markers including *Pax5* and *Bcl6* [39], indicating that expression of IL-10 can directly affect B cell differentiation pathways. Thus, Bregs are not a static B cell subset defined by specific cell surface markers, but rather comprise a dynamic subset of B cells that can be induced to exhibit regulatory functions in a context-dependent manner.

2. The role of IL-10 in PV pathogenesis

Pemphigus vulgaris (PV) is a tissue-specific autoimmune blistering disease caused by autoantibodies against the keratinocyte adhesion protein desmoglein (Dsg) 3[40]. Anti-Dsg3 IgG antibodies are both necessary and sufficient to cause characteristic suprabasal epidermal blisters in mouse passive transfer models of PV [41, 42]. Even monovalent anti-Dsg3 antibody fragments (Fab' or single chain variable fragment monoclonal antibodies) can induce blisters in mouse and human skin [43-45], thus clearly establishing the pathogenicity of anti-Dsg3 antibodies in PV.

Because of IL-10's diverse functions in regulating immune responses, there is great interest in understanding the role of IL-10 in the onset and treatment of autoimmunity. Recent studies have expanded our understanding of IL-10 in PV.

IL-10 in mouse models of PV

In a murine alloreactive model of PV, pathogenic and nonpathogenic Dsg3-reactive $CD4^+$ T cell clones (isolated after immunization of $Dsg3^{-/-}$ mice with Dsg3) have been isolated; the former induce anti-Dsg3 IgG production and typical PV blisters after adoptive transfer with splenic $Dsg3^{-/-}$ B cells to $Dsg3^{+/+}Rag\text{-}2^{-/-}$ mice, whereas the latter do not elicit disease [46]. IL-4 and IL-10 expression are significantly upregulated in pathogenic versus non-pathogenic anti-Dsg3 T cell clones. However, exogenous administration of IL-10 does not promote production of anti-Dsg3 IgG from primed B cells *in vitro*, and *in vivo* IL-10 blockade by expression of soluble IL-10 receptor does not affect disease incidence, whereas IL-4 promotes anti-Dsg3 IgG production and is necessary for disease onset in this model. In contrast, $IL\text{-}10^{-/-}$ mice demonstrate increased susceptibility to blister formation after passive transfer of PV plasma, and conversely, exogenous administration of IL-10 prevents blister formation after passive transfer of PV plasma to wild-type mice [47], indicating that IL-10 protects against PV blister formation. It is unknown whether these findings are due to loss of the immunoregulatory effects of IL-10, or whether IL-10-deficient keratinocytes may have defects in cell adhesion. In favor of the latter, IL-10 has been shown to inhibit the p38/MAPKAP-kinase 2 pathway [48], which protects against blister formation by regulating PV IgG-induced Dsg3 endocytosis in keratinocytes [49-52]. Taken together, these data are not sufficient to support a central role for IL-10 in the onset of autoimmunity in mouse PV models, although IL-10 may have other regulatory roles in preventing PV blister formation downstream of IgG binding to Dsg3.

IL-10 gene polymorphisms in PV patients

An increased frequency of the low producer IL-10 haplotype (−1082A/−819T) was identified in Argentinian PV patients, suggesting that the decreased production of IL-10 may predispose to PV, or alternatively that haplotypes conferring high and intermediate IL-10 production are protective against PV [53]. A weak association between PV and a different low producer IL-10 haplotype (−1082A/−819C/−592C) was also identified in Slovak PV patients [54]. How IL-10 polymorphisms might affect PV susceptibility in these patient populations is unknown, although the phenotype-genotype correlations are consistent with the protective role of IL-10 observed in mouse studies.

Serum levels of IL-10 in PV

Serum IL-10 levels have been reported to be elevated in PV patients with active disease compared to unaffected controls [55, 56], and in one study, levels of serum IL-10 correlate with disease activity [55]. However, two other studies were unable to detect serum IL-10 in PV patients [57, 58]. It is possible that the use of high-sensitivity assays in some studies may facilitate the detection of lower level increases in serum IL-10 in patients versus controls. IL-10 is consistently upregulated in the blister fluid of PV patients [55, 57], although elevations of IL-10 in blister fluid are also observed in bullous contact dermatitis, indicating that this finding is non-specific and likely results from local production of IL-10 by damaged keratinocytes.

IL-10 in IgG4 class switch

Although the Fc region of anti-Dsg3 IgG is not required for blister formation, active disease is associated with specific anti-Dsg3 IgG subclasses. PV patients with active disease demonstrate predominantly IgG4 followed by IgG1 autoantibodies to Dsg3, whereas patients in remission and unaffected relatives of PV patients can demonstrate anti-Dsg3 IgG1[59-63]. Furthermore, in patients with active disease, anti-Dsg3 antibodies comprise a significantly higher percentage of total serum IgG4 versus IgG1[64], indicating selective enrichment of PV autoantibodies in the IgG4 subclass.

IL-10 can induce naïve CD40-primed B cells to class switch and secrete antibody [65], preferentially of the IgG4 subclass [14, 66, 67]. IgG4 possesses unique structural features within the hinge region that prevent it from crosslinking antigen, forming immune complexes, or activating complement [68-70]. These anti-inflammatory functions of IgG4 in part underlie the effectiveness of allergen desensitization therapy. Repetitive antigen stimulation induces an influx of IL-10, made initially by T regulatory cells, then B cells and monocytes. IL-10 promotes the production of antigen-specific IgG4, which blocks the pro-inflammatory effects of IgE, and IL-10 also causes antigen-specific T cells to become anergic or exhausted (discussed further below) [14, 71, 72]. In beekeepers tolerant to bee venom antigens and patients after allergen-specific immunotherapy, IgG4 production has been shown to be restricted to IL-10^+ B cells [34].

Interestingly, novice beekeepers initially demonstrate IgG1 serum responses to phospholipase A antigens in bee venom, but within 3 years virtually all beekeepers have an IgG4-predominant response [73], similar to the evolution of autoantibody profiles in PV patients. Thus, repetitive antigen exposure triggers a stereotyped immune response, characterized by an increase in IL-10^+ T and B cells and a shift toward antigen-specific IgG4, which in the setting of allergy is protective. However, in the setting of PV, the switch to antigen-specific IgG4 does not alleviate disease, but instead becomes the defining serologic feature of active disease.

IL-10^+ T cells in PV

The critical role of Tregs in maintaining immune homeostasis is evidenced by individuals with IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome, caused by mutations in the Treg transcription factor FOXP3 [74]. Patients develop a broad range of autoimmune and inflammatory conditions, including enterocolitis, dermatitis, type 1 diabetes, and autoimmune thyroiditis. Subsequently, there have been numerous studies on the role of Tregs in autoimmunity. Tregs are reduced in patients with systemic lupus erythematosus, correlating with disease severity (reviewed in [75]). However, studies in type 1 diabetes, multiple sclerosis, and rheumatoid arthritis have not shown consistent changes in Treg frequencies in the peripheral blood, suggesting that qualitative rather than quantitative defects in Tregs, or Treg deficiencies in affected tissues, may be more important in these diseases. A complicating factor in determining the role of IL-10 in Treg function and autoimmunity is that IL-10 expression can occur in $FoxP3^-$ T cells and not all $FoxP3^+$ Tregs express IL-10 [31], indicating that IL-10 expression does not define the Treg population and conversely that Tregs do not always depend on IL-10 for their regulatory functions.

Studies in PV have shown that similar low frequencies of Dsg3-autoreactive T cells are found in PV patients and asymptomatic carriers of PV-associated HLA class II alleles, but not healthy HLA-unmatched controls [76]. There are no marked differences in Dsg3 peptides recognized by T cells from PV patients and HLA-matched unaffected individuals, indicating that T cell autoreactivity to Dsg3 is primarily dictated by HLA class II expression and is not sufficient to produce disease [77]. In contrast, IL-10^+ Dsg3-reactive Tregs, capable of suppressing T cell proliferation in response to Dsg3 in an IL-10-dependent manner, are found in 17% of PV patients, compared to 80% of HLA-matched unaffected controls [78]. Although FoxP3 expression was not directly assayed in these studies, collectively the data suggest that IL-10^+ Dsg3-reactive Tregs and T helper cells are critical for maintaining tolerance to Dsg3 and controlling disease onset in PV.

As discussed above, IL-10 production by T cells is critical for limiting host immune responses, but these protective functions can become detrimental in different contexts. During chronic viral infection, both CD4 and CD8 T cells can become functionally exhausted [79, 80]. These cells lose the capacity to eliminate target cells, secrete pro-inflammatory cytokines, and proliferate in response to antigen which results in the inability to control viral replication. IL-10 plays a critical role in mediating T cell exhaustion. In a mouse model of chronic lymphocytic choriomeningitis virus infection, treatment of mice with an IL-10 receptor blocking antibody reestablishes cytotoxic T cell functions and promotes viral clearance [81, 82]. Similarly, *in vitro* blockade of IL-10 signaling in exhausted CD4 T cells isolated from chronically infected HIV or hepatitis C individuals restores T cell proliferation and secretion of antiviral cytokines in response to antigen [83, 84]. Autoimmunity, like chronic infection, is characterized by the inability to clear antigen, leading to repetitive antigen stimulation and IL-10 induction. Although T cell exhaustion is detrimental in the setting of chronic infection, autoantigen-specific T cell exhaustion in PV would be desirable, as the blunting of immune responses by IL-10 may reestablish tolerance to self-antigen and potentially induce disease remission.

IL-10^+ B regulatory cells in PV

The functional significance of Bregs was first described in a mouse model of experimental autoimmune encephalomyelitis, in which recovery from disease was dependent on IL-10^+ autoantigen-reactive B cells [85]. B cells exhibiting regulatory functions have subsequently been identified in humans, where they are thought to be most highly enriched in the $CD19^+CD24^{hi}CD38^{hi}$ B cell subset [32]. The physiologic and pathophysiologic roles of Bregs have previously been reviewed [38, 86]. Pemphigus patients with active disease have an increased percentage of $CD19^+CD24^{hi}CD38^{hi}$ IL-10-expressing Bregs in the peripheral blood compared to unaffected controls or pemphigus patients in remission [87]. However, Bregs in pemphigus patients showed reduced ability to secrete IL-10 and suppress interferon-gamma expression by $CD4^+$ T cells. These findings are generally consistent with prior studies, which have identified an expansion of Bregs in other autoimmune disease patients [33], but with qualitative defects in Breg IL-10 production and T cell suppressive capacity [32].

A recent study has shown that pemphigus patients achieving long-term complete remission of disease after B-cell depletion therapy with the anti-CD20 monoclonal antibody rituximab demonstrate significantly higher numbers of IL-10-expressing $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs compared to unaffected controls or pemphigus patients in incomplete remission [88]. The elevation of $CD19^{+}CD24^{hi}CD38^{hi}$ transitional B cells in patients in long-term remission could simply reflect a delay in B cell repopulation due to more complete B cell depletion in responders. Alternatively, the expansion of IL-10^{+} Bregs in long-term responders may be an independent consequence of rituximab therapy, since B cell depletion causes a temporary rise in the levels of serum B cell activating factor [89], which can induce the transcription of IL-10 in B cells [90]. Thus, it is unclear whether prolonged remission after rituximab in PV is due to the absence of anti-Dsg3 antibody-secreting cells or requires the additional protective effect of IL-10^{+} Bregs. Supporting a direct role for IL-10^{+} Bregs in disease remission, a study of myasthenia gravis patients treated with rituximab showed that disease remission is associated with early B10 cell repopulation, whereas delayed B10 cell repopulation is associated with lack of response to therapy [91].

3. Therapeutic potential of IL-10 in PV

Due to IL-10's complex roles in maintaining immune homeostasis, the challenge for therapy is to understand the contexts in which IL-10 can be effectively and safely modulated to treat disease. Systemic lupus erythematosus (SLE) patients demonstrate elevated levels of IL-10 production by peripheral blood mononuclear cells [92, 93], elevations in serum IL-10 correlate with SLE disease activity [94, 95], and IL-10 gene polymorphisms conferring high IL-10 production are significantly associated with risk of developing SLE [96, 97]. An IL-10 blocking monoclonal antibody prevents onset of lupus-like disease in NZB/W F1 mice [98] and also reduces polyclonal IgM and IgG production by B cells isolated from SLE patients [99, 100]. These and other studies have led to the theory that SLE is a state of polyclonal B cell hyperactivity and that IL-10 may help drive disease by promoting the continuous differentiation of B cells into antibody-secreting cells, with their autoantibodies being one of the hallmark diagnostic features of SLE. Subsequently, a clinical trial of an IL-10 blocking monoclonal antibody in 6 SLE patients demonstrated clinical efficacy and safety, with decreased disease activity, decreased markers of immune cell hyperreactivity, and no serious adverse events at six months follow up [101].

Rheumatoid arthritis (RA) patients demonstrate many of the same features of disease as patients with SLE in regard to IL-10, including elevated IL-10 production by peripheral blood mononuclear cells [92], increased serum (as well as synovial) IL-10 levels [102], and decreased antibody secretion by B cells after IL-10 blockade [100], suggesting that IL-10 blockade could be similarly beneficial for the treatment of RA. However, in mouse models of collagen induced arthritis, transfer of CD40-primed, IL-10^{+} B cells prevents disease onset and also ameliorates established disease [103]. These effects are dependent on IL-10, since an IL-10 blocking monoclonal antibody inhibits the protective effects of IL-10^{+} B cells, and transfer of CD40-primed IL-$10^{-/-}$ B cells do not prevent disease onset. Additionally, *in vitro* culture of human RA synovial cells with IL-10 decreases their ability to act as antigen presenting cells [104], suggesting a suppressive role of IL-10 in this context. Based on the hypothesis that IL-10 would act as an anti-inflammatory and tolerogenic agent in RA, a trial

of subcutaneous IL-10 in six RA patients was performed. However, RA patients demonstrate no clinical benefit after IL-10 treatment [105]. IL-10 therapy is associated with increased Fc gamma receptor expression on monocytes and correspondingly increased tumor necrosis factor alpha production by monocytes after immune complex stimulation, as well as a non-significant trend toward elevated C-reactive protein levels, suggesting that IL-10 is not effective as a systemic anti-inflammatory agent in RA. As an alternative approach, targeted delivery of IL-10 to the sites of inflammation has proven effective in preclinical studies of RA [106], and a Phase I clinical trial to deliver IL-10 specifically to the synovium is currently underway [107]. These studies underscore IL-10's potentially beneficial and detrimental roles in regulating inflammation and the challenges involved in harnessing IL-10's biological functions to effectively treat disease.

IL-10 may also be a double-edged sword for PV. Ideally, IL-10 could be delivered to induce Dsg3-specific T cell exhaustion in order to attenuate the autoimmune response. However, IL-10 could also further stimulate anti-Dsg3 IgG4 production, and this in fact may be the predominant response early on in therapy, with tolerogenic effects occurring only after chronic administration. Alternatively, administration of IL-10 after B cell depletion may promote tolerance and avoid further stimulation of IgG4 class switch and antibody secretion due to prior depletion of the memory B cell pool. Such a strategy may help re-establish the immune regulatory network and prevent disease relapse after B cell depletion, which affects approximately 80% of PV patients treated with rituximab [88]. An additional strategy for therapy could be to restore IL-10's regulatory functions in Bregs and Tregs, which are thought to be dysfunctional in PV patients. Targeted re-expression of IL-10 in these cell subsets may be more effective than systemic IL-10, given its myriad and potentially conflicting roles in different cell types.

The dual nature of IL-10 in PV (detrimental during active disease but beneficial for disease remission) is depicted in **Figure 2**. Future studies are necessary to clarify the role of IL-10 in PV patients throughout the course of disease and therapy. A better understanding of the context-dependent roles of IL-10 in immune regulation may not only help improve our understanding of PV pathogenesis, but also lead to the design of novel strategies for disease treatment.

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Highlights

- The cytokine IL-10 has myriad functions in maintaining immune homeostasis
- IL-10 may have both harmful and beneficial regulatory roles in pemphigus vulgaris
- IL-10 based therapies in pemphigus vulgaris may be a novel strategy for treatment

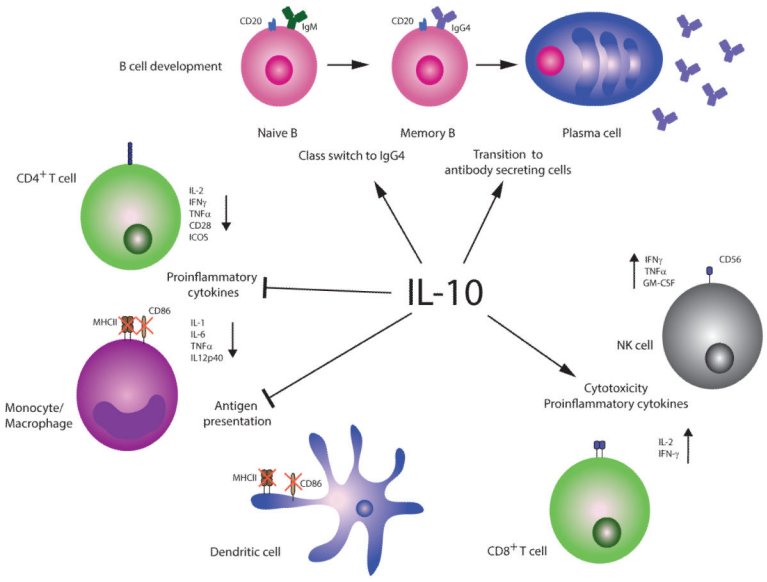

Figure 1. IL-10 in general immune homeostasis

IL-10 inhibits proinflammatory cytokine production, including IL-2, interferon gamma (IFNγ), and tumor necrosis factor alpha (TNFα) from $CD4^+$ T cells [7], as well as IL-1, IL-6, TNFα, and IL-12 production from monocytes and macrophages [8, 9]. IL-10 impairs $CD4^+$ T helper cell effector and memory responses by inhibiting CD28 and inducible costimulator (ICOS) T cell signaling [10] and downregulating major histocompatibility complex class II (MHCII) and CD86 costimulatory molecules on monocytes and dendritic cells, which prevents effective antigen presentation [11-13]. IL-10 expression in B cells favors class switch to IgG4 [14] and B cell differentiation into plasma cells [31], which can have anti-inflammatory effects due to IgG4's inability to fix complement or form immune complexes. Alongside these predominantly anti-inflammatory functions, IL-10 (in conjunction with IL-2) can increase cytotoxicity of $CD8^+$ T cells [16] and natural killer cells [18] by upregulation of pro-inflammatory cytokines, including IFNγ, IL-2, TNFα, and/or GM-CSF. However, long-term exposure of $CD4^+$ and $CD8^+$ T cells to IL-10 can result in T cell exhaustion [81, 82], including lack of cytotoxicity, cytokine production, and antigen-induced proliferation.

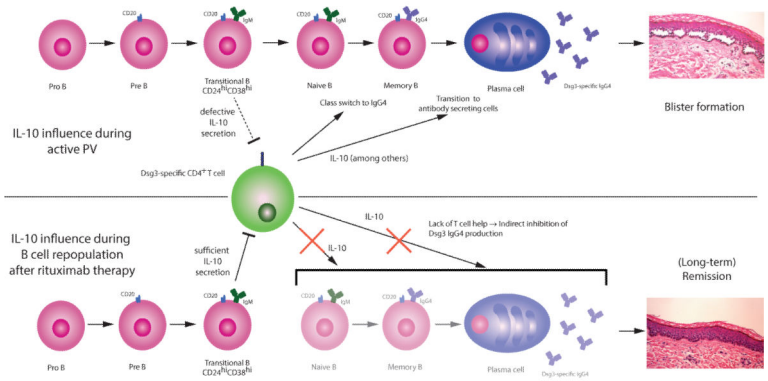

Figure 2. A model for the dual roles of IL-10 in PV during active disease and remission after B cell depletion therapy

In active disease, IL-10 favors class switch to IgG4, the characteristic PV autoantibody subclass. Additionally, B cell differentiation into antibody secreting cells is promoted by IL-10, which results in higher anti-Dsg3 antibody concentrations, leading to disease symptoms. Bregs in active PV are defective, with reduced IL-10 secretion and inability to suppress $CD4^+$ T cell responses, which perpetuates the autoimmune reaction. After B cell depletion with rituximab, repopulating $CD24^{hi}CD38^{hi}$ transitional B cells produce IL-10 that can inhibit $CD4^+$ T cells, thereby preventing the stimulation of pathogenic anti-Dsg3 B cell populations, leading to disease remission.