Bullous pemphigoid (BP) is the most common autoimmune blistering disease and is most prevalent in the elderly. BP is characterized by an inflammatory cell infiltrate, autoantibodies against the hemidesmosomal proteins BP180 and BP230 of basal keratinocytes and subepidermal blistering (Hammers and Stanley, 2016). BP180 is a transmembrane protein, while BP230 is an intracellular protein. Direct immunofluorescence staining reveals linear deposition of IgG and/or C3 and/or C5 at the dermal–epidermal junction. Various inflammatory mediators, including cytokines/chemokines and proteolytic enzymes, are present in lesional skin, blister fluids, and/or blood of BP patients.

As a transmembrane protein, BP180 is easily accessible to autoantibodies and it has been demonstrated to be pathogenically relevant in animal models of BP. Passive transfer of rabbit anti-mouse BP180 IgG or anti-BP180 IgG autoantibodies from BP patients into wild-type mice or BP180 humanized mice, respectively, induces skin disease, which recapitulates the key features of human BP. In these in vivo animal models, pathogenic anti-BP180 IgG binding to BP180 on basal keratinocytes triggers complement activation, mast cell degranulation, and infiltration and activation of neutrophils. Proteases released by infiltrating neutrophils cleave BP180 and other hemidesmosome-associated proteins, causing subepidermal blistering (Liu et al., 1993, 2000). Anti-BP180 IgG also causes BP180 depletion in hemidesmosomes, resulting in blister formation without complement activation. In addition, BP autoantibodies stimulate cultured keratinocytes to secrete IL-6 and IL-8.

### Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) comprises the pooled fraction of serum IgG from thousands of healthy blood donors. IVIG consists mainly of IgG1 and IgG2. Although IgG is the dominant fraction, IVIG also contains other Ig isotypes, such as IgA or IgM. IVIG has been used to treat many inflammatory and autoimmune diseases, including autoimmune blistering diseases, such as pemphigus, BP, and epidermolysis bullosa acquisita.

Numerous mechanisms have been proposed to explain the immunomodulatory effects of IVIG. For more comprehensive and in-depth information on IVIG, please refer to the excellent reviews by Gelfand (2012) and Schwab and Nimmerjahn (2013). Herein, we briefly summarize various modes of action of IVIG in IgG-mediated autoimmune diseases (Figure 1). These proposed modes of action include saturation of the IgG protective neonatal FcR receptor (FcRn), neutralization of autoantibodies by anti-idiotypic antibodies, neutralization of cytokines or modulation of cytokine production, attenuation of complement-mediated tissue damage, modulation of functions of Fc receptors, and modulation of effector functions of T, B, and dendritic cells (Gelfand, 2012; Schwab and Nimmerjahn, 2013).

### IVIG in BP

The mainstream therapy for autoimmune skin diseases, including BP, is high-dose systemic corticosteroids and immunosuppressive drugs. However, long-term treatment with these drugs causes many side effects and even death, and some BP patients are unresponsive to these treatments. Many case reports and a recent randomized double-blind trial of IVIG for BP proved IVIG to be a safe and effective therapy for this disease (Amagai et al., 2017).

Li et al. (2005) were the first to investigate the modes of action of IVIG in autoimmune cutaneous blistering disease using animal models of...
To further investigate the mechanisms of IVIG therapeutic activities in BP, Sasaoka et al. (2018) used two BP mouse models, passive transfer of anti-BP180 IgG into neonatal BP180-humanized mice, and adoptive transfer of human BP180-immunized spleen cells into adult immunodeficient BP180-humanized mice. In the former animal model, the authors pretreated neonatal mice with IVIG (400 mg/kg/day and 2,000 mg/kg/day dosages) followed by injection of polyclonal or monoclonal mouse anti-human BP80 IgG. IVIG at a 2,000-mg/kg/day dosage significantly reduced circulating mouse anti-human BP180 IgG levels and disease severity. Similarly, IVIG at a 2,000-mg/kg/day dosage also protected neonatal BP180-humanized mice from developing BP disease induced by BP IgG associated with significantly reduced circulating anti-BP180 IgG autoantibodies and reduced C3 deposition at the basement membrane zone. Although not directly tested, the reduction of pathogenic IgG in these models is likely through FcRn saturation by IVIG. These results confirm the findings by Li et al. (2005) and extend these findings to the IgG passive transfer models induced by mouse IgG against BP180 and BP IgG autoantibodies.

Neonatal mouse passive transfer is a quick and simple approach for testing proof of principle in a preventive setting, but is technically difficult to evaluate the efficacy of a drug (here IVIG) in a therapeutic setting. Therefore, the authors of this article employed their spleen cell adoptive transfer model of BP. In this model, wild-type mice are immunized by grafting human BP180 transgenic mouse skin. Immunized spleen cells are subsequently transferred intravenously into adult immunodeficient BP180-humanized mice. The recipient mice develop clinically significant skin lesions on day 14, and the disease scores peak 35 days post adoptive transfer (Ujiie et al., 2010). The spleen cell adoptive transfer model was used to test the efficacy of IVIG in three treatment regimes; intravenous administration of IVIG from day 1 to day 21 daily, from day 1 to day 5 daily, and from day 6 to day 10 daily post spleen cell adoptive transfer. Similar to results obtained in the IgG passive transfer models, all three IVIG treatments significantly reduced disease scores more than saline control mice at all time points examined from day 14 to day 35.

IVIG modulates production of cytokines/chemokines (Gelfand, 2012). IVIG down-regulates proinflammatory cytokines, such as TNF-α, IL-1 and IL-6, and up-regulates the anti-inflammatory cytokine IL-10. To determine whether IVIG has the same activity in experimental BP, the authors first examined plasma cytokine/chemokine levels in both IgG passive transfer and spleen cell adoptive transfer models. IVIG treatment significantly reduced IL-6 levels in both IgG passive transfer and spleen cell adoptive transfer models of BP, and significantly increased IL-10 in the spleen cell adoptive transfer model. The authors then demonstrated that IVIG also significantly reduced the release of IL-6 by BP IgG-stimulated HaCaT cells, an immortalized human keratinocyte cell line. These in vitro and in vivo data suggest that IVIG can also act on keratinocytes and other local and/or immune cells to regulate production of IL-6 and IL-10 in BP. These findings are clinically relevant since IL-6 and IL-10 levels are associated with disease activity in BP (D’Auria et al., 1999; Inaoki and Takehara, 1998).

The work by Sasaoka et al. (2018) shows that, besides the increase of pathogenic IgG clearance by saturation of FcRn and the neutralization of pathogenic IgG by anti-idiotypic antibodies, IVIG may directly modulate keratinocyte and immune cell production of critical cytokines/chemokines in BP. Several important questions remain to be answered. For example, is FcRn required for IVIG activity in the spleen cell adoptive transfer model of BP? Does IVIG negatively regulate autoreactive B cells as another mechanism underlying the reduced level of pathogenic anti-BP180 IgG in the spleen cell adoptive transfer model of BP? IVIG is an effective therapy for BP through multiple mechanisms. A better understanding of the modes of action of IVIG should improve the efficacy of IVIG, either as a monotherapy or as a component of combined therapy.
A Hairy Tale of Monocytes and Contact Hypersensitivity Reactions

Benjamin Voisin¹,², Thomas Doebel¹,² and Keisuke Nagao¹

Hair follicles have recently emerged as immunologically active organs that orchestrate recruitment and trafficking of immune cells within skin. Liu et al. (2018) expand our knowledge in this growing area of research by characterizing the network of immune cell interactions during experimental contact hypersensitivity that, interestingly, is centered around hair follicles.

Immunity at body surfaces involves an intricate network of immune cell interactions that rely heavily on innate mechanisms initiated in the epithelium. Such interactions are multidirectional and may involve various immune and non-immune cell types of the epithelium and subepithelial layers that facilitate the propagation of effective immune responses. For example, perturbation of skin mediated by mechanical stress, allergens, or microbes may provoke keratinocytes to produce chemokines and cytokines that recruit and activate immune cells. Cytokines that are produced by activated immune cells, such as monocytes/macrophages (TNF), dendritic cells (IL-23), or lymphocytes (IL-17, IL-22) may also act on the epidermis to enhance the production of host-protective soluble factors, such as antimicrobial peptides. Hair follicles (HFs) have recently emerged as immunologically functional structures that mediate skin-specific regulation of the immune system. Interactions that involve HF are also not unidirectional and they may involve positive- and negative-feedback loops, many of which are uncharacterized. We have shown previously that minor mechanical stress leads to the production of CCL2 and CCL20 in the upper regions of HFs. These chemokines then mediate CCR2- and CCR6-dependent recruitment of monocyte precursors of epidermal Langerhans cells (Nagao et al., 2012). HFs also support epidermal resident memory T-cell persistence by constitutively producing cytokines IL-7 and IL-15 (Adachi et al., 2015). Building on their previous work demonstrating that regulatory T cells preferentially localized around HFs (Gratz et al., 2013), Ali et al. (2017) recently showed that skin-resident regulatory T cells were a source of the Notch ligand, Jagged 1, that promoted HF stem cell proliferation and differentiation. Thus, the follicular microenvironment provides a niche for tissue-immune crosstalk that is crucial not only for immunological homeostasis, but tissue homeostasis as well.

REFERENCES

1Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland, USA

2 These authors contributed equally to the work.

Correspondence: Keisuke Nagao, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bldg 10, Room 12N240B, 10 Center Drive, Bethesda, Maryland, 20892-1908, USA. E-mail: keisuke.nagao@nih.gov

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In aggregate, Liu et al. (2018) provide evidence for an antigen recognition-dependent immunological cascade during CHS, in which HFs seem to mediate the encounter and interaction of immune cells involved.

The work by Liu et al. (2018) expands our knowledge on HF-immune system crosstalk. Utilizing o xoalzone...