Autoimmunity and Type 2 Inflammation Play a Critical Role in the Pathophysiology of Bullous Pemphigoid

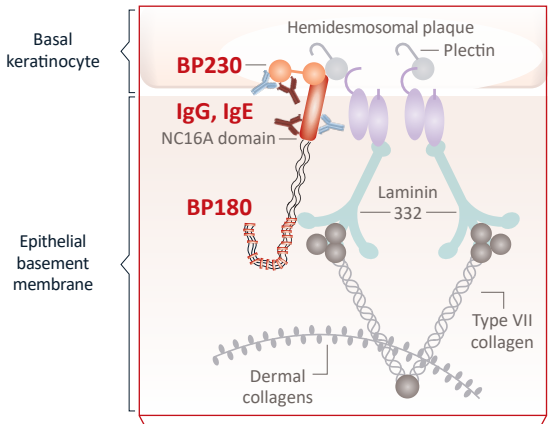
Autoimmunity triggers an inflammatory response that involves innate and adaptive pathways and leads to the clinical manifestations of BP.[1-3]

Autoantibodies against BP180 and BP230 are a hallmark of BP[1,4]

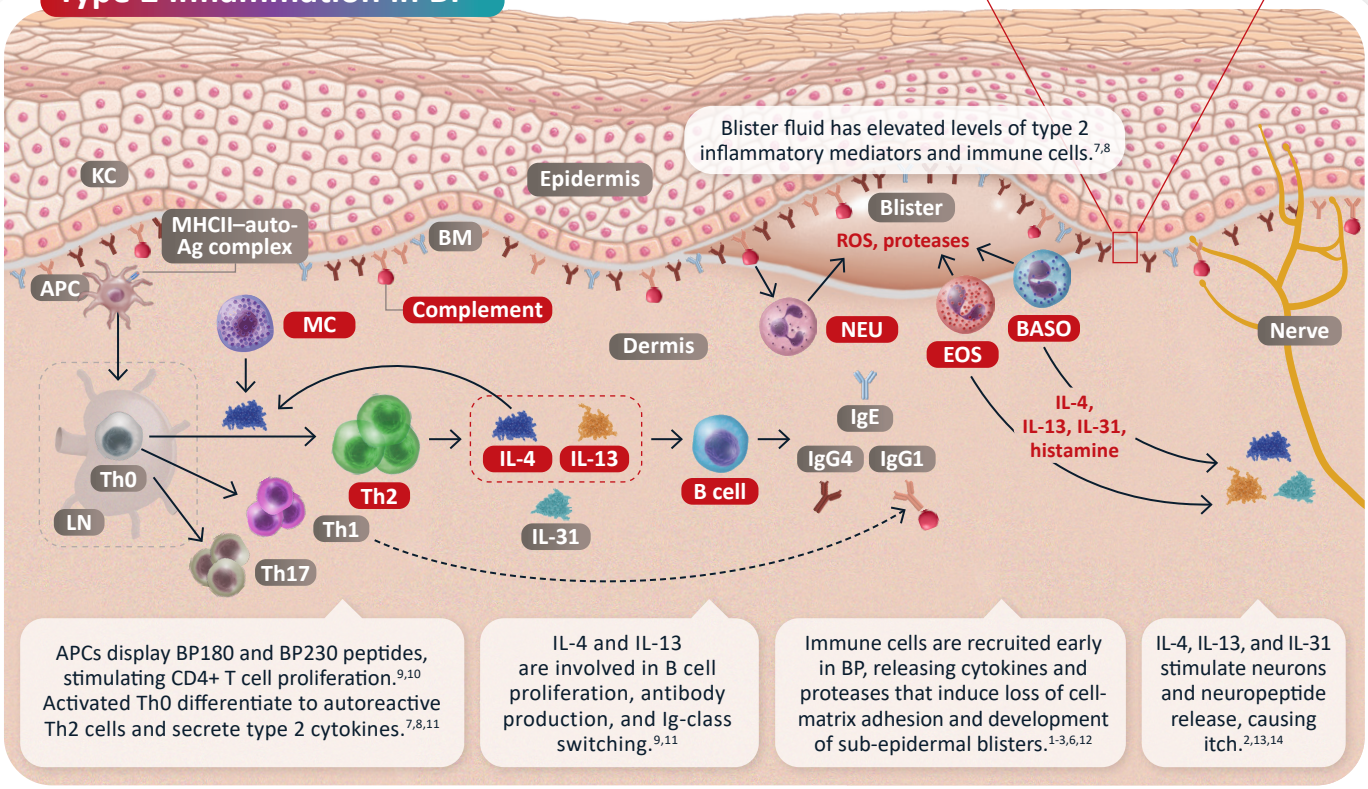
The transmembrane protein **BP180** and the intracellular protein **BP230** contribute to adhesion of basal keratinocytes to the dermal-epidermal junction.[1,4]

BP180 and **BP230** are part of the complex structure of the hemidesmosome, whose role is to keep the epidermis attached to the dermis.[1-3]

IgG and **IgE** autoantibodies against **BP180** and **BP230** trigger inflammation and blister formation through complement-dependent and -independent pathways.[1,2,5,6]



Type 2 Inflammation in BP*



APCs display BP180 and BP230 peptides, stimulating CD4+ T cell proliferation.[9,10] Activated Th0 differentiate to autoreactive Th2 cells and secrete type 2 cytokines.[7,8,11]

IL-4 and IL-13 are involved in B cell proliferation, antibody production, and Ig-class switching.[9,11]

Immune cells are recruited early in BP, releasing cytokines and proteases that induce loss of cell-matrix adhesion and development of sub-epidermal blisters.[1-3,6,12]

IL-4, IL-13, and IL-31 stimulate neurons and neuropeptide release, causing itch.[2,13,14]

This process leads to the formation of polymorphous lesions and dermal-epidermal splitting, causing blistering.[2,5,6,12]

*The roles of various cells and mediators in BP continue to be clarified by the results of translational research studies.

Ag, antigen; APC, antigen-presenting cell; BASO, basophil; BM, basement membrane; BP, bullous pemphigoid; CD, cluster of differentiation; EOS, eosinophil; Ig, immunoglobulin; IL, interleukin; KC, keratinocyte; LN, lymph node; MC, mast cell; MHCII, major histocompatibility complex II; NC16A, noncollagenous domain 16A; NEU, neutrophil; ROS, reactive oxygen species; Th, T helper.

1. Schmidt E, Zillikens D. *Lancet.* 2013;381(9863):320-332. **2.** Cole C, et al. *Front Immunol.* 2022;13:912876. **3.** Kasperkiewicz M, Zillikens D. *Clin Rev Allergy Immunol.* 2007;33:67-77. **4.** Hertl M, et al. *J Clin Invest.* 2006;116(5):1159-66. **5.** Cole C, et al. *Antibodies (Basel).* 2022;11(3):44. **6.** Hammers CM, et al. *J Invest Dermatol.* 2020;140(4):733-741. **7.** Kowalski EH, et al. *Autoimmun Rev.* 2019;18(5):526-534. **8.** Gounni Abdelilah S, et al. *Clin Immunol.* 2006;120(2):220-231. **9.** Zhang J, et al. *J Invest Dermatol.* 2018;138(9):1917-1924. **10.** Ujiie H, et al. *Clin Immunol.* 2012;142(2):167-75. **11.** Fang H, et al. *Autoimmun Rev.* 2020;19(11):102661. **12.** Thoma-Uszynski S, et al. *J Immunol.* 2006;176(3):2015-23. **13.** Hashimoto T, et al. *J Am Acad Dermatol.* 2020;83(1):53-62. **14.** Garcovich S, et al. *Vaccines.* 2021;9(3):303.

ADVENT dermatology

ADVENT is a breakthrough educational program bringing together different specialties treating patients with type 2 inflammatory diseases.

Prof. Thomas Bieber, Dermatologist, Germany

Autoimmunity and Type 2 Inflammation Play a Critical Role in the Pathophysiology of Bullous Pemphigoid

- Autoimmunity triggers an inflammatory response that involves innate and adaptive pathways and leads to the clinical manifestations of BP[1-3]
- Autoantibodies against BP180 and BP230 are a hallmark of BP[1,4]
  - The transmembrane protein BP180 and the intracellular protein BP230 contribute to adhesion of basal keratinocytes to the dermal-epidermal junction[1,4]
  - IgG and IgE autoantibodies against BP180 and BP230 trigger inflammation through complement-dependentand -independent pathways[1,2,5,6]
- Dysregulated type 2 immunity contributes to itch, inflammatory lesions, and blister formation in BP[2,6,7,11,14]
  - Antigen-presenting cells process and display peptides of BP180 and BP230, stimulating CD4+ T cell proliferation[9,10]
  - Activated naive T cells differentiate primarily to autoreactive Th2 cells and secrete type 2 cytokines, including IL-4, IL-13, IL-31, and IL-5[7,8]
  - IL-4 and IL-13 are involved in B cell proliferation, antibody production, and Ig-class switching[9,11]
  - Immune cells, namely neutrophils, eosinophils, mast cells, and basophils, are recruited to the site of inflammation, releasing reactive oxygen species, cytokines and proteolytic enzymes that induce loss of cell-matrix adhesion and development of sub-epidermal blisters[1-3,6,12]
  - IL-4, IL-13, IL-31, and histamine, released by these immune cells, stimulate neurons and neuropeptide release, causing itch[2,13,14]
  - Blister fluid and serum have elevated levels of type 2 inflammatory mediators and immune cells[7,8]
- This process contributes to the formation of polymorphous lesions and dermal-epidermal splitting, causing blistering[2,5,6,12]

What is the ADVENT program?

ADVENT is a global medical education program that shares the latest evidence on diseases with underlying type 2 inflammation

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DERMATOLOGY	PULMONOLOGY	RHINOLOGY	GASTROENTEROLOGY
Atopic dermatitis	Asthma	Chronic rhinosinusitis with nasal polyps	Eosinophilic esophagitis
Prurigo nodularis	Chronic obstructive pulmonary disease		
Chronic spontaneous urticaria			
Bullous pemphigoid			

Goals of the platform

- Inform patient care
- Facilitate cross-specialty knowledge sharing
- Educate on implications of underlying type 2 inflammation
- Increase the knowledge of diseases driven by underlying type 2 inflammation

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