Basic principles of the immune system and autoimmunity

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Basic Principles of the Immune System and Autoimmunity

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Learning Objectives

After studying this chapter, you should know:

- The difference between the innate and adaptive immune system
- The functions of antigen presenting cells, B- and T-lymphocytes
- Causes of autoimmunity and types of hypersensitivity with emphasis on pemphigoid and pemphigus

The Immune System: A Short Introduction

Two Systems: The Innate and Adaptive System

The immune system is composed of two closely collaborative systems, an innate and an adaptive system (Fig. 1.1). *The immune system is composed of an innate and an adaptive system* These systems are activated as the first barriers of defense, mucosa and skin, are breached. The innate immune system is a constitutive present system that can act rapidly to eradicate microbes. *The innate system is a quick response system.* The primary cells of the innate immune system are macrophages, granulocytes, natural killer (NK) cells and dendritic cells, but other cells like epithelial cells can also be part of it. For instance macrophages and granulocytes are capable of phagocytosis of microorganisms by endocytosis. Pathogen-associated molecules are present on microbes and recognized by cells of the innate system by binding to toll-like receptors. In particular these cells are effective against bacteria whereas NK cells are used to fight viruses. They do this in an indirect way by recognizing and killing virally infected host cells. Besides the cellular response many proteins play an important part in the innate immune system, e.g. chemokines, interleukins, interferon and tumor necrosis factor. Binding of microbial antigens will therefore not only induce phagocytosis but also release of cytokines, which will result in an inflammatory response. Apart from these proteins the complement system constitutes an important part of the immune system. This system can be activated directly by a microorganism itself or indirectly by binding to antibodies produced by the adaptive immune system. Eventually proteins of the complement system promote phagocytosis and inflammation.

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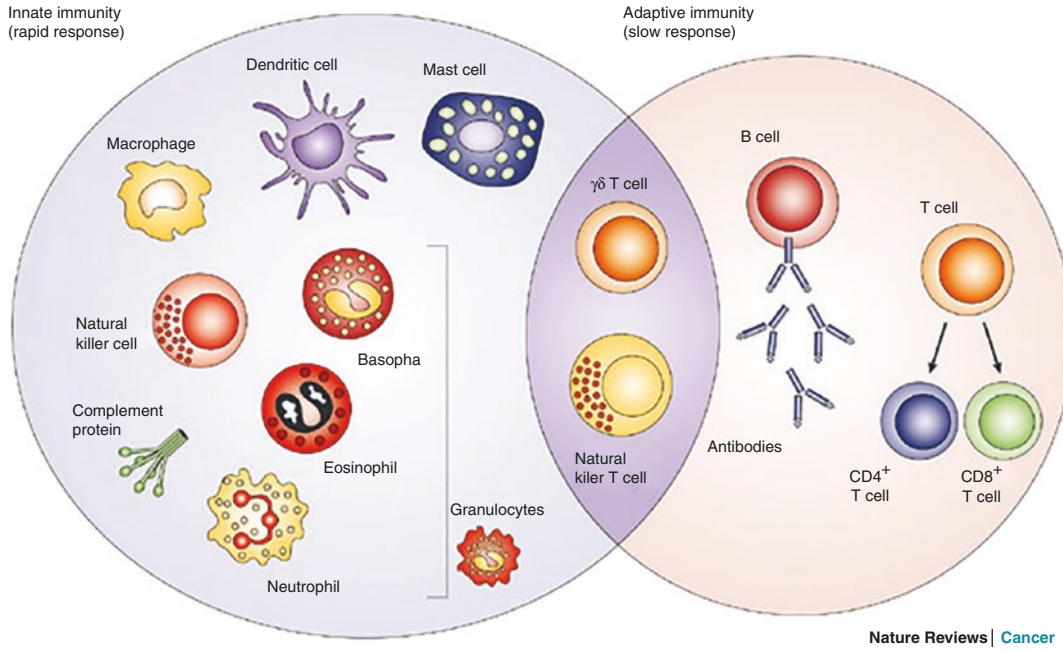

Fig. 1.1 An overview of the innate and adaptive immune system. [Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer, Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. **4**, 11–22. Copyright 2004]

The Adaptive System in More Detail

Next to the innate system is the adaptive immunity that can be divided in a humoral and cellular system (Fig. 1.2). *The adaptive immune system is divided in a humoral and cellular system and is an antigen specific system*. By definition the adaptive immunity is a "learning" system that has to be trained. In consequence the start will be slow, but once trained, the responses will also be quite fast. In contrast to the innate system, this system is antigen specific and by that more effective. An antigen as part of a microorganism or own cells, most frequently represents a protein, but it is good to know that it also can be a carbohydrate, lipid or DNA, all being capable of inducing an antibody response.

Lymphocytes bear antigen receptors on their surface and can on basis of these receptors be divided into B-lymphocytes and T-lymphocytes. These receptors are called the B cell receptor (BCR) or cell surface immunoglobulin in B-lymphocytes and the T cell receptor (TCR) in T-lymphocytes. *B- and T-lymphocytes are the main constituents of the adaptive immune system* B-lymphocytes originate directly from and also undergo some steps of maturation with assembly of the BCR within the bone marrow, whereas T-lymphocytes start in the bone marrow but the assembly of their TCR takes place in the thymus (Fig. 1.3). After recognizing an antigen by the BCR in the peripheral lymphoid tissues such as a lymph node, B-lymphocytes are activated and altered into plasma cells and large quantities of antibody are processed and secreted by these specific B-cells. These antibodies have the same antigen-binding site as the BCR that first recognized the antigen. Antibodies can inactivate an antigen, e.g. a microorganism by complement binding or aid in phagocytosis of this microorganism, the latter called opsonization. This is entire process is thus called humoral immunity.

T-cells are part of the cellular immunity, which basically is important in eliminating intracellular microorganisms, mainly viruses. In contrast to the BCR, the T-cell receptor can only recognize

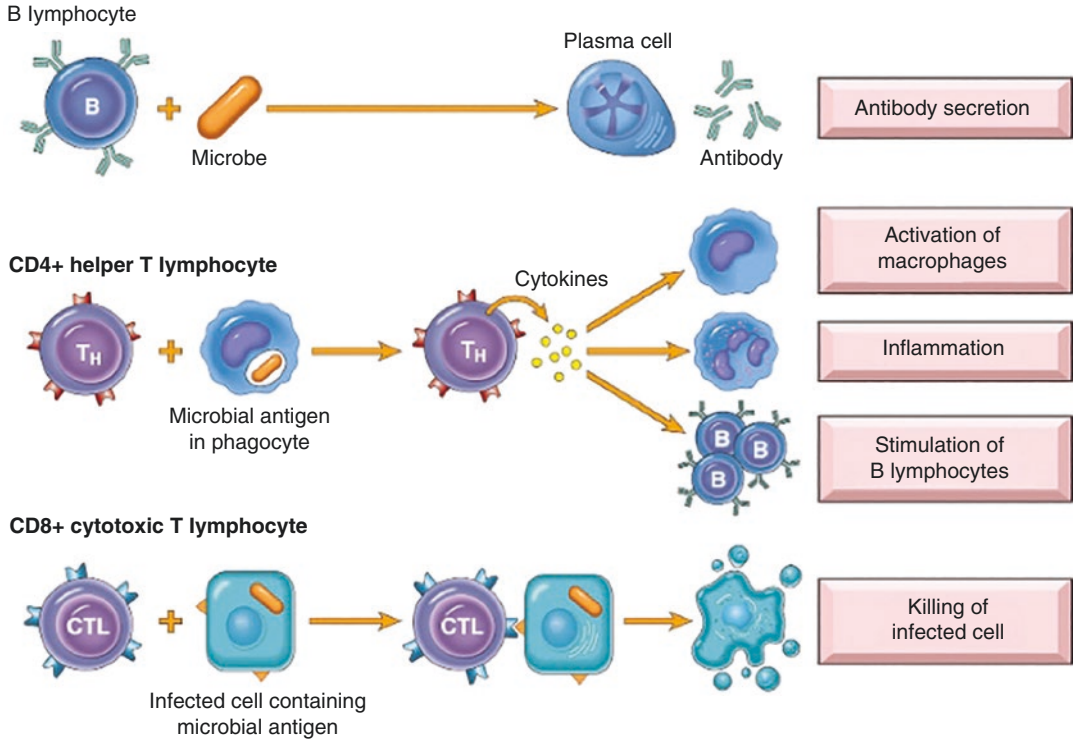

Fig. 1.2 The principle classes of lymphocytes and their functions in adaptive immunity. [Reprinted with permission from: Kumar V, Abbas AK, Fausto N, Aster J. Robbins & Cotran Pathologic Basis of Disease, 8th Edition, page 185, Copyright Elsevier 2010]

small fragments of proteins (peptide) that are presented on the surface of the infected cell by major histocompatibility complex (MHC) molecules, also called human leucocyte antigens (HLA). Thus microorganisms first have to be degraded before they can be recognized by the system. MHC molecules are divided into class-I and class-II molecules. Class-I molecules are present on all nucleated cells and platelets. Only a physical combination of an antigen-peptide within a specific MHC-I-class molecule can be recognized by the T-cell receptor. This activation transforms this particular T-cell into a cytotoxic T-cell capable of killing virally infected cells by inducing apoptosis.

MHC-II-class molecules are only expressed on certain cells of the immune system, in particular dendritic cells, macrophages and B-lymphocytes, together called antigen-presenting cells. These cells can present antigen-peptides in conjunction with MHC-II molecules to T-helper cells. These antigens are derived from degraded microorganisms that are phagocytized by the antigen-presenting cells. In addition, these T-helper cells can secrete numerous cytokines, thereby inducing activation of macrophages, stimulation of B-cells to produce antibodies but also cytotoxic T cells to do their work. T-helper cells can therefore functionally be divided into Th1 cells, stimulating a cytotoxic T-cell response, Th2 cells, involved in the humoral immune response, and different subsets of regulatory T-cells, involved in controlling these processes. *T-lymphocytes can be divided in cytotoxic T-cells and T-helper cells*. Importantly the interaction between the antigen presenting cells and the T cells with interaction between HLA molecules TCR's is helped by many other receptors and ligands on these cells, generally called "costimulatory molecules".

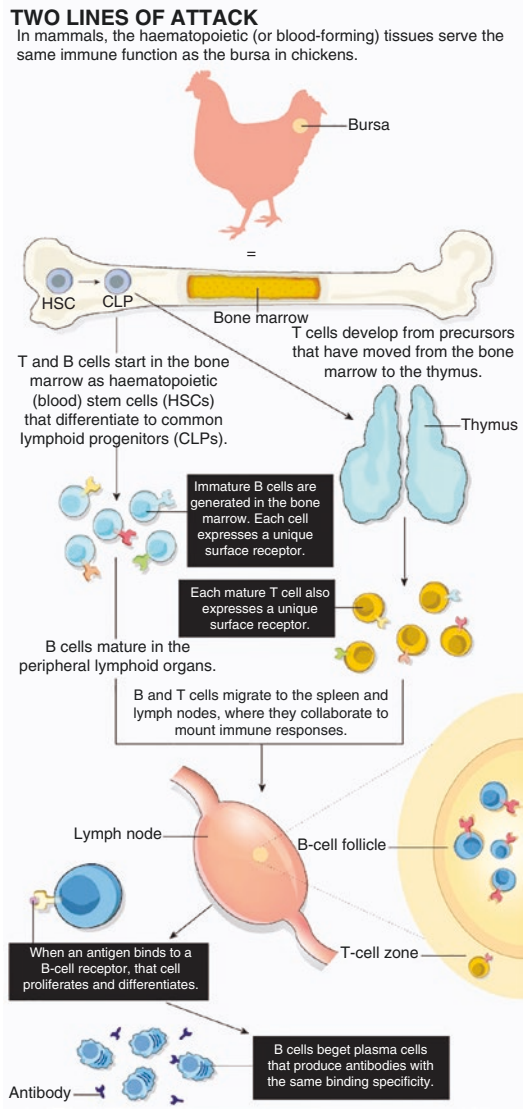

Fig. 1.3 The origin and fate of B- and T-lymphocytes. [Reprinted by permission from Macmillan Publishers Ltd: Nature, Gitlin AD, Nussenzweig MC. Fifty years of B-lymphocytes. 517, 139–141. Copyright January 2015]

Antibodies are produced by plasma cells, which are terminally differentiated B-lymphocytes (Fig. 1.4). *Antigen-specific antibodies are produced by plasma cells, which are terminally differentiated B-lymphocytes*. Each antibody is unique and produced by a single clone of plasma cells. Antibodies are composed of an antigen binding fragment (Fab) and a constant region (Fc), responsible for the effector function of the antibody. An antibody is made up of two identical heavy chains and two identical light chains. Both chains can be divided into a variable part, involved in antigen recognition, and a constant part. This constant part of the heavy chain divides the antibodies into five classes: IgM, IgA, IgG, IgE and IgD. Immature B-cells express IgM (sometimes in combination with IgD) class antibodies on the cell surface. However, under influence of cytokines B-cells can produce other classes of immunoglobulins, a process called isotype switching. This takes place in a specialized compartment of the lymph node, called the follicle or germinal center. In this compartment an additional process takes place, which is called affinity maturation and which means that binding of the BCR of individual B-cells to the antigen is further improved. B-cells with these improved receptors will more efficiently recognize the antigen after rechalllenge and therefore provide a better and faster immune response, which is the idea behind the effect of boost vaccinations in all vaccination programs. While B-cells that did not encounter an antigen before are called naive B-cells, these improved B-cells are called memory B-cells.

As already mentioned, the function of free antibodies is twofold: microorganisms loaded with antibodies are phagocytized more easily because phagocytizing cells are capable of binding the Fc part of the antibodies. Besides that, once fixed to an antigen, antibodies are capable of stimulating the complement system. *Antibodies aid in phagocytosis of microbes and stimulate the complement system.*

All cells of the immune system originate from the bone marrow. The myeloid stem cells mature into granulocytes, macrophages, erythrocytes and thrombocytes, while lymphoid stem cells differentiate to precursor B- and T-cells (and natural killer cells not discussed here). Maturation of B-cells occurs in the bone marrow with formation of unique antigen receptors on the cell surface. In contrast, maturation of T-cells takes place in a specialized organ, called the thymus. It is important that B- and T-cells do not react against

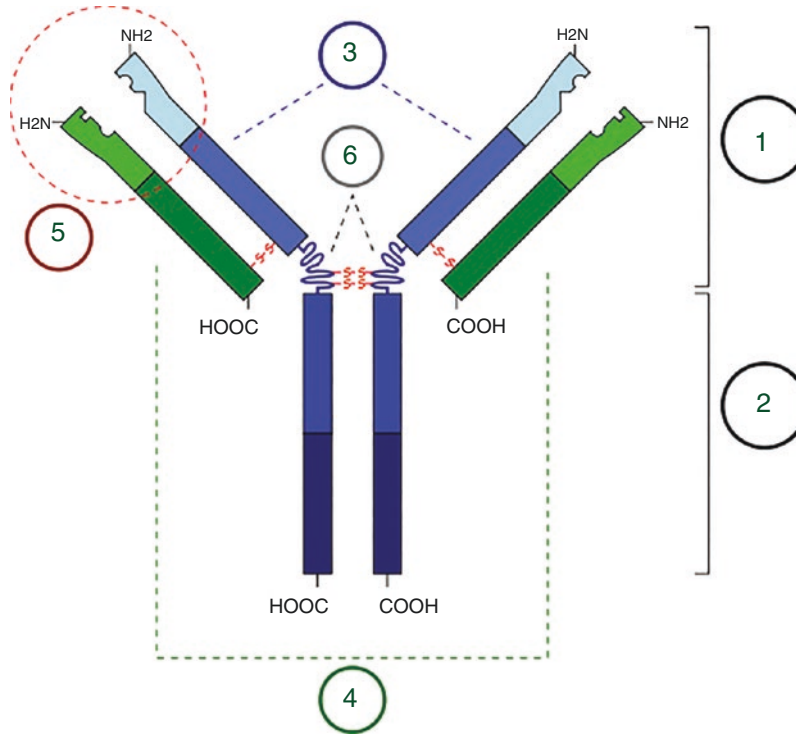

Fig. 1.4 Basic structure of an antibody. [Adapted from Y_tambe: Wikipedia under a Creative Commons Attribution-Share Alike 3.0 License.]

self-antigens, since this might result in autoimmunity. Normally, these potentially auto-reactive and therefore dangerous cells go into apoptosis, a process called negative selection or clonal deletion. After maturation in the bone marrow and thymus the lymphoid cells migrate to secondary lymphoid organs, e.g. lymph nodes, spleen and mucosa associated lymphoid tissues.

Whereas intact microorganisms can be transported directly to be presented to the B-cells in these tissues, for interaction with T-cells transport of antigens is mostly done by dendritic cells. In these peripheral lymphoid organs both the already mentioned naïve and faster and more efficient memory B- and T-cells reside, which can directly be activated.

A Closer Look at the Skin

Besides having a barrier function, the skin itself is also an important immunogenic organ. *The skin functions in the innate as well as in the adaptive immune system*. The skin possesses an innate immune response, characterized by synthesis and release of antimicrobial peptides like defensins and substance P. Next to the innate immunity, the adaptive immunity is provided by Langerhans cells, a population of dendritic cells that reside in the epidermis. These Langerhans cells can phagocytize antigens, migrate to regional lymph nodes (sometimes called veiled cells), and present the antigen to a T-lymphocyte, which can result in a cellular or humoral immune response, the latter only if the antigen is also presented to B-cells. Moreover, circulating macrophages, T-cells and dendritic cells, present in the dermis, provide continuous immunological surveillance.

Autoimmunity

Cells of the innate immune system recognize so-called pathogen associated molecules on microorganisms. Human cells lack these patterns on their surface, thereby preventing auto-reactivity.

The adaptive immune system avoids auto-reactivity by the aforementioned clonal deletion or negative selection. This result is also called immunological tolerance. When this tolerance is breached, auto-reactive B- and T-cells might be formed, a process called autoimmunity. *Auto-reactive B- and T-lymphocytes can induce auto-immune diseases*. Immunological tolerance can be achieved by central tolerance, i.e. clonal deletion of B- and T-cells in bone marrow and thymus respectively, and peripheral tolerance. Peripheral tolerance is achieved by functional inactivation and active suppression of auto-reactive mature B- and T-cells that have escaped clonal deletion. *Central and peripheral tolerance prevents auto-immunity*. For complete activation of B- and T-cells, besides antigen-antibody binding, the already mentioned co-stimulatory signals are also necessary. These co-stimulatory signals are mostly present on cells of the innate system, i.e. macrophages and dendritic cells. Absence of these signals, e.g. in case of auto-reactivity, will result in functional inactivation of the immune response. This is called anergy. Regulatory T-cells (Tregs) play an important role in active suppression of the immune response by inhibitory effects on T-cells, macrophages and dendritic cells. In addition to stimulation, some of these costimulatory molecules have an opposite effect by dampening the immune interaction, a physiological process necessary to stop an immune reaction. One of these molecules is CTLA4. Interestingly, some recently developed drugs interact with these costimulatory interactions, for instance Ipilimumab, which blocks CTLA4, is presently used to improve the immune reaction against metastatic melanoma.

Unfortunately these mechanisms are not perfect and auto-reactivity can still occur and might eventually result in autoimmune diseases. Several mechanisms can be responsible for breaching immunological tolerance. First, certain microorganisms can bind to the constant part of membranous IgM on the cell surface of B-lymphocytes, thereby avoiding the need of co-stimulatory signals of T-helper cells. This is called a superantigen stimulated polyclonal lymphocytic activation. In addition, the Epstein-Barr-virus (EBV), after internalization, stimulates B-cell proliferation and inhibits apoptosis by producing certain proteins, like EBNA-2 and EBNA-LP. These mechanisms result in an uncontrolled polyclonal B-lymphocyte response that might produce self-reactive antibodies. Second, antigens of microorganisms might have a strong resemblance to self-antigens. This might result in a cross reaction of B- and T-cells against auto-antigens, a process called molecular mimicry. Finally, exposure of the immune system to normally shielded antigens (eye, testis, brain) or exposure to newly formed antigens (neoepitopes) can result in an immune response to a self-antigen that has not previously been recognized as such. An example of a neoepitope in blistering diseases is the shed ectodomain of collagen XVII that might serve as a self-antigen.

Important modulating factors in autoimmunity are sex hormones, explaining the predominance of autoimmune diseases in women, and genetic background. *Sex hormones and genetic background are important factors for developing autoimmune diseases.* In particular MHC genes are an important factor in developing autoimmune diseases. Associations have been found between certain MHC haplotypes and autoimmune diseases. For instance, HLA-DQβ1*0301 has been associated with various variants of pemphigoid, whereas several studies have demonstrated an association between HLA-DRB1 and pemphigus vulgaris.

Various pathophysiological mechanisms in autoimmune diseases are eventually responsible for the clinical manifestations. These hypersensitivity reactions are classified after the proposal of Gell and Coombs. In Type II reactions auto-antibodies are directed against cell or matrix components. Pemphigoid and pemphigus are the result of type II hypersensitivity. *Autoimmune blistering diseases are the result of type II hypersensitivity, whereas systemic lupus erythematosus results from a type III hypersensitivity reaction.* A Type III reaction is the result of

deposition of antigen-antibody immune complexes in various organs, eventually resulting in tissue destruction. An example of a type III hypersensitivity reaction is systemic lupus erythematosus (SLE). Typically, SLE is more prominent in women and genetic factors contribute to the disease. SLE is characterized by the formation of IgG antibodies against nuclear antigens (ANA), in particular against double stranded DNA (dsDNA). These circulating IgG-dsDNA complexes deposit in various organs, especially in kidneys (glomerulonephritis), skin (facial erythema) and joints (synovitis). These immune complexes are the mediators of tissue injury, mainly by activating the complement system. As shown in Fig. 1.5, these complexes can directly be visualized by immunofluorescent techniques in a skin biopsy of the patient. Such a pattern is also called a lupus band. In fact, complement consumption and low levels of circulating complement factors C3 and C4 characterize disease activity.

Type IV hypersensitivity or delayed type hypersensitivity is the result of stimulation of Th1-lymphocytes, that can induce tissue damage by secretion of certain cytokines. Eczema is an example of a type IV reaction.

As stated above pemphigoid and pemphigus are the result of a type II hypersensitivity reaction. In bullous pemphigoid autoantibodies are directed against collagen XVII (BP180) and/or BP230, important components of the hemidesmosome, responsible for attachment of the epidermis to the dermis. *Pemphigoid diseases are characterized by antibodies against hemidesmosomal components*. These antibodies are mainly of the IgG class, although often in conjunction with IgA. These circulating autoantibodies react with these hemidesmosomal antigens, giving rise to a cascade of events. Binding of IgG to BP180 results in complement activation, attraction of inflammatory cells to the dermis and release of proteases by granulocytes that ultimately induce dermal-epidermal splitting [1] (Fig. 1.6). Besides this inflammatory response another mechanism has been proposed responsible for detachment of the epidermis from the dermis. Adhesion of antibodies to BP180 can result in internalization and endocytosis of this protein, thereby weakening the hemidesmosome (Fig. 1.7) [2]. In this case an inflammatory response is not necessary for subepidermal blistering and explains the existence of pemphigoid blisters without an inflammatory infiltrate.

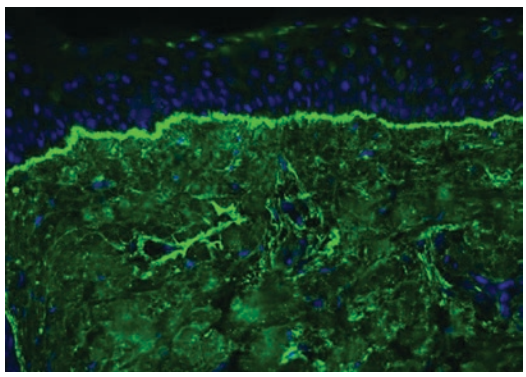

Fig. 1.5 The lupus band: deposition of immunoglobulins along the basement membrane zone

Also pemphigus is caused by autoreactive antibodies, in this case directed against desmoglein 1 and 3. *Pemphigus is characterized by antibodies against desmosomal proteins, mainly desmogleins.* Desmogleins are components of the desmosome, responsible for the attachment between keratinocytes. The exact mechanism by which these antibodies are responsible for acantholysis and subsequent intraepidermal blistering is not completely clear. In contrast to pemphigoid an inflammatory response seems not to be primarily responsible. Several alternative theories have been proposed. First is the steric hindrance theory, which is based on the idea that direct interference of IgG with the extracellular domain of desmoglein results in acantholysis [3]. The second theory implies that deranged cell signaling, i.e. activation of p38 MAPK [4], RhoA [5] and plakoglobin [6], interferes with desmosomal function. Finally, pemphigus IgG might influence desmosome assembly and disassembly. Binding of IgG to desmoglein could result in internalization of desmoglein by endocytosis, eventually reducing the adhesion strength between keratinocytes [7].

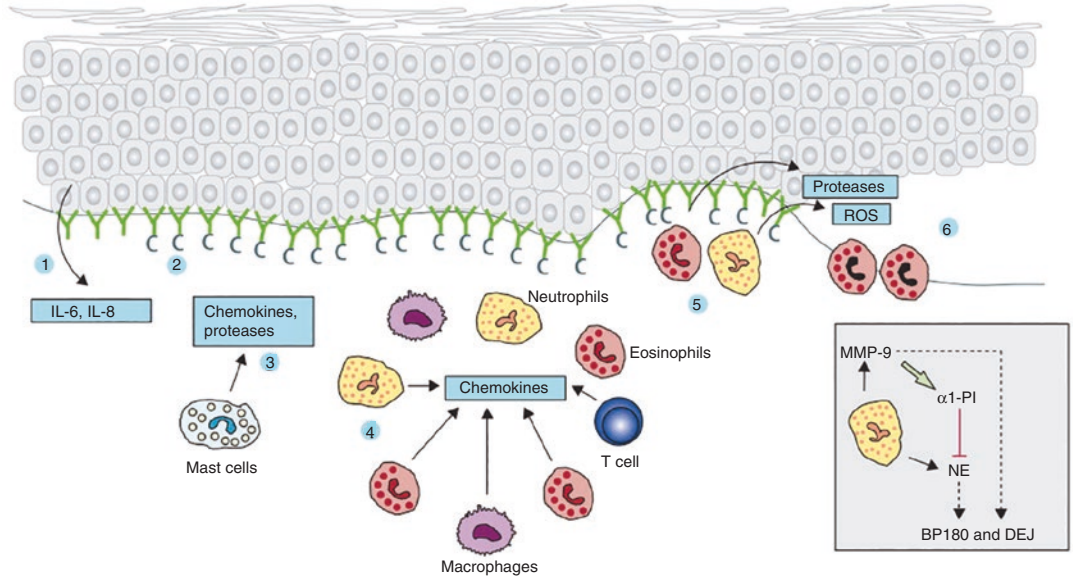

Fig. 1.6 Hypothetical sequence of events leading to blister formation in bullous pemphigoid. Binding of autoantibodies to BP180 initiates Fc receptor-independent events leading to the release of interleukin 6 (IL-6) and IL-8 from basal keratinocytes (1). Complement is activated (2) at the dermal–epidermal junction (DEJ) and mast cells degranulate (3). Complement activation and chemokine gradients result in the infiltration of inflammatory cells into the upper dermis (4). Secretion of inflammatory mediators further increases the inflammatory reaction before granulocytes at the DEJ release proteases (insert) and reactive oxygen species (ROS) (5) that ultimately induce dermal–epidermal splitting (6). As shown in the neonatal mouse model of bullous pemphigoid, matrix metalloproteinase 9 (MMP-9) secreted from neutrophils cleaves (green arrow) α1-proteinase inhibitor (α1-PI) to remove neutrophil elastase inhibition (red bar). Both MMP-9 and NE also directly degrade proteins of the DEJ including BP180 (insert). [Reprinted from The Lancet, 381, Schmidt N, Zillikens D, Pemphigoid diseases 320–332, with permission from Elsevier.]

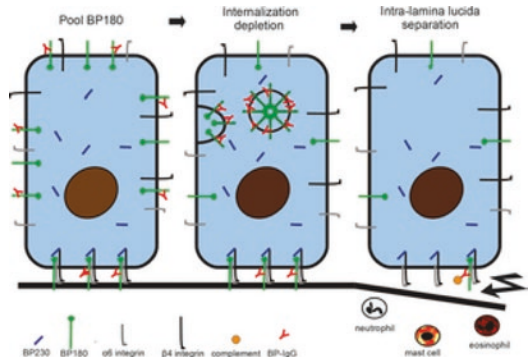

Fig. 1.7 Potential mechanisms of blistering in BP. Hemidesmosomal proteins are distributed homogeneously on the plasma membrane, and some of them compose HD at the ventral side of basal cells (left). HD seemed to be constantly remodelled, assembly and disassembly. Initially, autoantibodies bind to BP180, which is distributed on the plasma membrane of basal cells, and lead to internalization of BP180 and depleting BP180 from the plasma membrane (middle). The depletion of BP180 by anti-BP180 autoantibodies may disturb the supply of BP180 and impair HD formation. Insufficient HD lacking BP180 may not have enough adhesional strength to basement membrane. Finally, intra-lamina lucida separations may be caused by mechanical stress or inflammation, such as fixation of complement and FcgR-dependent activation of neutrophils, induced via Fc fragment of pathogenic IgG (right). [Reprinted from: Iwata H, KitajimaY. Bullous pemphigoid: role of complement and mechanisms for blister formaation within the lamina lucida. Exp Derm 2013; 22:381–385. With permission from Wiley.]

Review Questions

1. The innate immune system
   a. Is an antigen-specific system
   b. Is a quick response system
   c. Is made up of mainly lymphocytes
2. B-lymphocytes
   a. Are efficient in killing viruses
   b. Mature in the thymus
   c. Differentiate into plasma cells, which produce antibodies
3. Autoimmune blistering diseases
   a. Can be the result of a disturbed peripheral tolerance
   b. Are an example of type III hypersensitivity
   c. Both answers are true

Answers

1. b
2. c
3. a

References

1. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013;38:320–32.
2. Iwata H, Kitajima Y. Bullous pemphigoid: role of complement and mechanisms for blister formation within the lamina lucida. Exp Dermatol. 2013;22:381–5.
3. Heupel WM, Zillikens D, Drenckhahn D, Waschke J. Pemphigus vulgaris IgG directly inhibit desmoglein 3-mediated transinteraction. J Immunol. 2008;181:1825–34.
4. Berkowitz P, Hu P, Warren S, Liu Z, Diaz LA, Rubenstein DS. p38MAPK inhibition prevents disease in pemphigus vulgaris mice. Proc Natl Acad Sci U S A. 2006;103:12855–60.
5. Waschke J, Spindler V, Bruggeman P, Zillikens D, Schmidt G, Drenckhahn D. Inhibition of Rho A activity causes pemphigus skin blistering. J Cell Biol. 2006;175:721–7.
6. Caldelari R, de Bruin A, Baumann D, Suter MM, Bierkamp C, Balmer V, Müller E. A central role for the armadillo protein plakoglobin in the autoimmune disease pemphigus vulgaris. J Cell Biol. 2001;153:823–34.
7. Aoyama Y, Kitajima Y. Pemphigus vulgaris-IgG causes a rapid depletion of desmoglein 3 (Dsg3) from the Triton X-100 soluble pools, leading to the formation of Dsg3-depleted desmosomes in a human squamous carcinoma cell line, DJM-1 cells. J Invest Dermatol. 1999;112:67–71.

Suggested Further Reading

Robbins and Cotran. Pathologic basis of disease. Saunders, 9th edition.
Abbas and Lichtman. Cellular and Molecular Immunology. Saunders 8th edition.