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Immunological skin diseases: Boundaries and relationships

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Abstract

About half of skin diseases are immune-related. Immunological skin diseases are crudely divided into infectious, allergic, autoimmune and other types based on the etiology, pathogenesis and immune responses. While their distinction is not absolute, cause-effect and inter-relationship exist among them. This review focuses on the intrinsic associations among different categories of skin immune diseases, in the aim to help in the understanding and investigation of etiological factors and interventional strategies for skin immune diseases.

Introduction

Immunology essentially is the study of body's defense against infection. The immune system is typically divided into two categories–innate immune response and adaptive immune response. Any disruption/defects of the immune system can result in immunological skin diseases. Excessive and undesirable immune responses can cause hypersensitivity or autoimmune diseases, while hypoimmunity can lead to infectious diseases and skin tumor. Hypersensitivity reactions were classified into four broad types: type I, type II, type III and type IV, based on the mechanisms involved. Rough clustering and classification of immunological skin diseases, which groups skin diseases based on their general features in common, is of great value in the treatment and research of these skin diseases. However, accumulating basic and clinical evidence showed that there were no clear boundaries among infectious diseases, hypersensitivity reactions, autoimmune diseases and skin tumors, and among which an intricate relationship do exist. A full understanding of the relationship among these immunological skin diseases will help us explore innovative preventive,diagnostic, therapeutic approaches from the etiological and pathogenetic point of view.

Skin microbiota, skin infections and hypersensitivity

The skin/mucosa surface is resided by a host of micro-organisms including bacteria, fungi, viruses, chlamydiae as well as protozoa. Many of them are bacteria, of which there are more than 100 species on human skin, with numbers in the millions. More than 99% of these bacteria cannot be detected by conventional cultivation techniques [1]. These resident floras and the skin constitute a complex ecosystem in which interactive and interdependent relationships exist between microbial constituents, and between microbes and the host. The populations of microbial inhabitants and their abundance vary in various regions of the skin. Clinical and epidemiological data have suggested that bacterial infections were the cause of some type I hypersensitivity reactions (eg: urticarial) and type III hypersensitivity reactions (eg: allergic cutaneous vasculitis). Atopic dermatitis, an allergic skin disease, is often closely associated with abnormal epidermal barrier function and dysregulated immunity (especially Th1/Th2, Th2/Th2, Th1/Th17) [2,3]. Patients with atopic dermatitis have an increased susceptibility to skin infections and cutaneous colonization. The *Staphylococcus aureus* colonization rate was higher in atopic dermatitis patients compared to the normal controls [4]. A number of cell surface and secreted virulence factors produced by S. *aureus* among which superantigens, peptidoglycan, lipoteichoic acid could activate many immune cells, have a close association with some diseases [5]. Superantigens are an extraordinary family of non-glycosylated low molecular weight exoproteins (molecular sizes ranging from 19-30 kDa) secreted by some human pathogenic bacteria. The superantigens are unusually resistant to heat, acids, desiccation and proteolysis. It has been suggested that superantigens contributed to the pathogenesis of atopic dermatitis due to the following observations and findings. 1) There was a strong correlation between the severity of atopic dermatitis and the number of superantigen-secreting *S. aureus* colonizing the skin; 2) In some atopic dermatitis patients, significant levels of IgE antibodies against superantigens which could be secreted by *Staphylococcus aureus* were found on their skin. The presence of these IgE antibodies to superantigens correlates with skin disease severity. 3) Topical application of staphylococcal enterotoxin B to skin could induce eczema-like lesions, which may be caused by SEB through binding of MHC II molecules on antigen presenting cells or stimulation of T cells to produce proinflammatory cytokines. Superantigens induce T cell to express skin homing receptor via stimulation of IL-12 production. T regulatory cells witnessed a loss of immunosuppressive activity after being challenged by the superantigen SEB. Superantigens could induce corticosteroid resistance and, has the ability to induce T cells to secrete IL-31. In summary, superantigens participate in the pathogenesis of AD via multiple immune pathways.

Recent studies have shown that δ-toxin produced by *S. aureus*

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induces mast cell degranulation both in vivo and in vitro. Similar with IgE-crosslinking-mediated mast cell degranulation, δ-toxin-induced mast cell degranulation depended on calcium (Ca^{2+}) influx, but they have different signaling pathways. The former does not require the spleen tyrosine kinase (Syk), while the latter does. The isolates of *Staphylococcus aureus* from the skin of atopic dermatitis patients produced δ-toxin.

The mice, inoculated with δ-toxin producing *S. aureus* and then challenged once with ovalbumin (OVA), became more inflammatory at the site of inoculation and produced higher level of serous OVA-specific IgE than those inoculated with δ-toxin-deficient *S. aureus* and then challenged once with ovalbumin (OVA). Further investigations found that δ-toxin promote inflammation via activation of mast cells [6]. Taken together, colonization of *S. aureus* in some patients with atopic dermatitis may be a trigger factor- the products of *S. aureus* play a pathogenic role in the development of atopic disease.

Staphylococcus epidermidis is a normal resident of the human skin. *S. epidermidis* on skin surface plays a protective role in skin immunity [7]. *S. epidermidis* was unable to secrete superantigens, but produced a low level of δ-toxin [6]. Recently, we have found that HIV infection and non-viral infections-related patients have a higher level of colonization rate of *S. epidermidis* on the lesions of seborrheic dermatitis in their face than healthy individuals. The topical application of antibiotics achieved the same symptomatic relief rate as topical tacrolimus could do. These observations have suggested that a higher rate of colonization of *S. epidermidis* in the face may play a role in the pathogenesis of seborrheic dermatitis [8], however, its underlying mechanism remains to be investigated.

Viral infection and tumor immunity

It is estimated that approximately 40 percent of human tumors are viral infections related. Human papillomaviruses (HPVs) are responsible for many cutaneous/mucous growths. It has been commonly accepted that high-risk HPVs increase the risk of developing several cancers, such as that of the cervix and oropharynx. Some HPV vaccines have been successfully used to prevent infection with certain high-risk types of HPVs. HPV vaccines-which elicit neutralizing antibodies against human papillomavirus, preventing viruses from entering into epithelial cells (The antibody titer elicited by vaccination was exponentially 1-4 times higher than natural infection)-greatly reduce those vaccinated the risk of infection [9]. The HPV vaccine launch a new era in tumor prevention by vaccination.

Keratinocytes are main target of HPV infection. Innate immunity is the first line of defense against infection. When infected by HPV, keratinocytes could be induced to produce a series of cytokines, chemokines, adhesion molecules etc. Other sentinels of skin immune system, such as Langerhans cells, natural killer cells, natural killer T cells, other dendritic cells were also mobilized to form a pro-inflammatory microenvironment, and set the stage for subsequent adaptive immune response. Natural killer cells could directly kill virus-infected cells [10].

HPVs have developed complicated methods to evade host immune responses through a long history of evolution, which include: absence of antigen for processing and presentation, modification of antigen presenting cells which comprises the ability of antigen presentation, avoidance of the response to IFN-α, inhibition of production of various cytokines and chemokines, structural similarities between virus proteins and cellular proteins (eg: E7 and XP-g complementing protein and RB binding protein 1), which enable virus proteins escape to be recognized by immune system [11]. Elucidation of interactions between host immune responses and HPV could aid in the pursuit of novel immunotherapies for treating HPV infections. Imiquimod, anagonist of toll like receptor 7 can activate keratinocytes and antigen presenting cells, mounting effective adaptive responses against HPV [10]. Local hyperthermia could effectively clear HPV-infected lesions through promoting interferon expression, apoptosis of keratinocytes and migrational maturation of Langerhans cells [12-16].

Merkel cell carcinoma is a rare cutaneous carcinoma with neuroendocrine differentiation, which has been suggested that Merkel cell carcinoma had strong association with polyoma virus infection [17]. Human herpesvirus 8 has been found to contribute to the development of Kaposi's sarcoma as well as EB virus to some lymphoma [9].

Viral infection has a close association with the development of autoimmune diseases, which has been relatively thoroughly studied. Clinical and epidemiological data have shown that viral infections were involved in the pathogenesis of several autoimmune diseases in genetically predisposed settings, for example, cytomagavirus, Epstein-Barr virus, parvovirus B19 have been-identified to increase susceptibility to systemic lupus erythematosus. EBV elicit autoimmune antibodies through molecular mimicry. The autoantibodies against the nuclear antigen of EBV, PPPGRRP, cross-react with PPGMRPP, the initial epitope of SmB. Immunization of mice with PPPGRRP or PGMRPP was able to elicit the production of autoantibodies against the Smith antigen (Sm). Other epitopes also have similar cross-reactivity to induce autoantibodies. EBV also triggered abnormal T cells responses, such as increased interferon-producing $CD4^+$ T cells, defective $CD8^+$ T cell immunity. Increased IFN-α in SLE and overexpression of IFN-associated genes were "interferon signature" of SLE. Virus stimulates high levels of IFN-α production in immature dendritic cells (mostly plasmacytoid dendritic cells). IFN-α promotes TLR expression of B cells, cell apoptosis, and release of auto-antigens RNA or DNA immune complex. Self-reactive B cells induced by EBV through molecular mimicry react with auto-antigens released from apoptotic cells, presenting the information of RNA auto antigens to RLR7, further stimulating auto-reactive B cells to proliferate and then produce autoantibodies. The complex of auto-antibodies and auto-antigens binds to the IgG-Fc receptors on the surface of plasmacytoid dendritic cells, further amplifying the production of IFN-α, which forms an endless loop of antiantibodies production [18,19]. In specific genetic settings, coxsackie virus, parvovirus, entericvirus, retrovirus and human T-leukemia virus are suspected of being the culprits of dermatomyositis. Inoculation of mice with coxsackie virus could replicate human polymyositis-like symptoms on the mice. Viral infection has also been reported to involve in the development of anti-phospholipid antibody syndrome and rheumatoid arthritis [19].

Autoimmunity and allergic diseases

Celiac Disease (CD) is an autoimmune disorder of the small intestine characterized by permanent intolerance to wheat gliadins and other cereal prolamins in the small bowel mucosa in genetically susceptible individuals, and it can be manifested cutaneously as dermatitis herpetiformis and other skin problems. Serologically, anti-transglutaminase antibodies to the enzyme tissue transglutaminase (tTG) are characteristically found in most patients. Histopathological changes include granular IgA deposition along the basement membrane and dermal papillae. CD patients were most often associated with other mucocutaneous diseases with features of other autoimmune or allergic diseases. Skin diseases associated with CD are divided into four

categories: autoimmune, allergic, inflammatory, and miscellaneous. Dermatitis herpetiformis, alopecia areata, cutaneous vasculitis, atopic dermatitis, urticarial and psoriasis were more frequently reported cutaneous manifestations associated with CD. The literature on the pathogenesis of cutaneous manifestations associated with CD was very limited [20].

Conclusions

Fighting against infection is the primary function of immune system. Given its strategic location in human body, skin plays an important and intrinsic role in skin immunity against infections. With the rapid development of metagenomics, we are becoming more and more knowledgeable about diversity and complexity of the microbiota on the surface of skin, mucosa, and respiratory tract. The interactions between microbiota and host, the pathogenic role of microbiota are increasingly being in-depth investigated. Environmental microorganisms, the metabolites or virulence factors of microorganisms which act directly upon skin or penetrate into skin or impair innate/adaptive immune responses could be pathogenic to skin and human body. It was reasonable to classify immunological skin diseases on the basis of immunological status, which provides useful guidelines for dermatologists and researchers in the understanding of pathogenesis, natural course of diseases, prognosis, and intervention of immunological skin diseases. In the face of the great stride in the temporary clinical medicine and immunology, we shall keep in mind that different immunological skin diseases by no means were separate entity, and they can be interdependent. Only from the molecular point of view based on cellular level research, can these intricate relationships be fully elucidated in the future, which will provide theoretical basis for prevention and treatment of these immunological skin diseases.

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