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Invited review article

Classification of inflammatory skin diseases: A proposal based on the disorders of the three-layered defense systems, barrier, innate immunity and acquired immunity

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We dedicate this manuscript to Dr. Yoshiki Miyachi, Professor and Chairman of the Department of Dermatology, Graduate School of Medicine, Kyoto University, from 1998 to 2014.

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ABSTRACT

The host defense system of the skin is composed of (1) a barrier, (2) innate immunity, and (3) acquired immunity. Inflammatory skin diseases can be classified into one of the disorders of these layers of the defense system, unless there is an ordinary response to specific infectious agents or internal/external injury. Any inflammatory skin disease partly simulates the response to real infections or dangers. Disorders of acquired immunity can be classified into (1) immunodeficiency, (2) immunohyperactivity (allergy), and (3) qualitative disorder (autoimmunity). Disorders of innate immunity can be classified into (1) innate immunodeficiency, (2) innate immunohyperactivity (general or local autoinflammation), and (3) qualitative disorder (general or local innate autoimmunity). The barrier of the skin is composed of (1) the physical barrier and (2) the chemical barrier. Several diseases, such as atopic dermatitis, are attributed to the disorder of these components of the barrier. Here, we propose an algorithm to classify the pathology of inflammatory skin diseases by means of what disorder in the specific layer of the host defense system is truly responsible.

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1. Layers of the host defense system

The host defense system of the skin is mainly composed of the following three layers: (1) barrier of the skin, (2) innate immunity, and (3) acquired immunity [1]. In general, these layers are aligned in this order chronologically, functionally, and phylogenetically. A disorder in a specific layer can arise from defects in the superior layer. Each layer has unique roles to protect the body against specific infectious agents and external/internal dangers. Inflammation is defined as a series of protective and regenerative responses of the body. Therefore, inflammatory skin diseases are originally a result of these protective and regenerative responses of the skin against infections and dangers. If primarily causative infections and dangers are ruled out, the dermatitis is due to hereditary or acquired disorder in a specific layer of the host defense system.

Descriptive dermatology of the morphological phenomena of skin has been developed for more than two thousand years. Despite recent and ongoing progress in immunology, innate immunity, and the skin barrier, inflammatory skin diseases have not yet been fully classified in terms of the defects in each layer of the host defense system.

In this review, we propose a new algorithm to understand the pathology of inflammatory skin diseases in terms of the specific roles of each three layer in host defense system of the skin (Box). We describe the disorder of these layers in reverse order from acquired immunity to barrier, for the better understanding (see Section 5). Physiological disorders of the body machine can be divided into quantitative disorders and qualitative disorders. We classified the disorders of this dichotomy, except for the disorder of barrier, whose understanding is insufficient for this classification (Table 1). This classification proposed here would be effective to clarify the current problems and the directions of research in this field.

2. Disorder of acquired immunity in skin diseases

2.1. Immunodeficiency

A number of hereditary diseases have been identified as a genetic lack of the specific molecules that are essential in acquired immunity. Many of them are associated with a variety of cutaneous infections and inflammation. For example, X-linked agammaglobulinemia (XLA) develops furunculosis, impetigo, and atopic-like eczematous eruptions. X-linked lymphoproliferative (XLP) disease is highly accompanied by infectious mononucleosis due to Epstein–Barr virus (EBV) infection. Chronic mucocutaneous candidiasis (CMCC) is composed of heterogeneous diseases, some of which have molecular defects in the acquired immunity, such as defects in the autoimmune regulator (AIRE) gene (see Section 2.3.1) [2]. Acquired immunodeficiency syndrome (AIDS) patients are highly susceptible to fungal and herpes virus infection, such as human herpes virus 8 (HHV8), and patients develop repetitive and severe herpes and Kaposi's sarcoma in the skin.

Box 1. Core of the new classification of inflammatory skin diseases.

- Inflammation is defined as a series of protective and regenerative responses of the body.
- Host defense system of the skin is composed of a barrier, innate immunity and acquired immunity.
- Three layers of the protection drive the most suitable response against infectious agents and external dangers whereas the basic response at the transcriptional level in the cell is very limited.
- Disorder of the specific layer of the host defense system of the skin can induce an inflammatory skin disease, which partly simulates the actual protective response against infections and dangers.

2.2. Immunohyperactivity/allergy

Another face of acquired immunity is an antitoxin, which neutralizes toxic agents such as venoms and poisons from insects, worms, and plants in nature [3]. However, hyperactivity of acquired immunity to a specific antigen results in allergic diseases. An allergy can be divided into two groups by the course of sensitization. One is an allergy with irritative and destructive sensitization, such as allergies to wasps and poison ivy. Another is an allergy without remarkable damages on the body at the sensitization phase, such as food allergies, and allergies to the cosmetic and industrial materials. The former allergy is originally beneficial and protective for species, whereas the latter is not.

As for the skin, allergic contact dermatitis is thought to have originated as a beneficial response in the skin, to eliminate toxic molecules and harmful insects and worms by oozing, acanthosis, hyperkeratosis, and exfoliation in the epidermis, accompanied by scratching behavior. However, a new material that has not exposed to organisms, as well as a new exposure condition of the existing materials for an ethnic, such as manufactured metals and peanut oil in industrial materials, can accidentally elicit acquired immunity in limited responders. Most people commonly inherit the former allergy, which is usually associated with irritant dermatitis by toxic allergens at the sensitization phase [3]. However, the latter allergy has not yet been phylogenetically inherited or eliminated for thousands of years, regardless of whether it is beneficial or not. Thus, the latter allergies to cosmetic materials, industrial products, and unspecified materials suffer limited people only since specific events in the history of specific ethnic groups.

2.3. Autoimmunity

Autoimmunity is a qualitative disorder mainly due to trouble within the organization of immune tolerance, which is essential for acquired immunity. Both central tolerance in the thymus and peripheral tolerance in extrathymic tissues are indispensable to avoid severe systemic autoimmune diseases. Here, two basic questions are raised. (1) Is a breakdown of the tolerance a primary disorder of acquired immunity or a secondary disorder attributed to the preceding layers of the host defense system in 'classical' systemic autoimmune diseases? (2) Are there any antigen-specific