

Review Article

Clinical and Experimental Research of Inflammatory Skin Diseases

Tetsuya Higuchi*

Department of Dermatology, Toho University Sakura Medical Center, Chiba, Japan

ABSTRACT: Skin is the largest organ of the whole body, and the main function of the skin is to protect it from the external environment, both physically and immunologically. As an immune system, immune-mediated responses in the skin lead to skin eruptions, including papules, vesicles, and erythema. There are various chronic immune-mediated skin disorders, such as atopic dermatitis and psoriasis. Recent progress in understanding the mechanisms underlying these diseases has led to new treatment options, such as biologics or small-molecule kinase inhibitors. In this review, our clinical and experimental results on inflammatory skin diseases are referred to. In patients with Sjögren's syndrome, anti-SS-A antibody-related annular erythema is developed mainly on the face, whereas superficial spongiotic annular erythema is exhibited on the extremities. CD40 ligand (CD40L) is ectopically expressed on B cells in patients with systemic lupus erythematosus (SLE) and lupus-prone mice. With the analysis of CD40L transgenic mice, it is suggested that excessive CD40L signaling leads to the development of SLE. CD40L detection with flow cytometry in T cells in drug eruption patients is expected to diagnose the causative drug. Psoriasis is associated with obesity via various adipokines. We found that leptin production is upregulated in subcutaneous adipose tissue in patients with obese psoriasis and associated with disease activity. In inflammatory bowel disease patients, various skin eruptions are found in the clinical course, and evaluation and treatment by a dermatologist are important. As an approach to treating inflammatory skin disease, we investigated dextran nanoparticles, including antigen and dendritic cell activators, to enhance the antigen-specific immune response in mice.

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Introduction

Various skin eruptions reflect pathological changes in the epidermis and dermis. The most common skin eruption, erythema, is caused by the dilation of dermal vessels

accompanied by surrounding inflammatory cells. Therefore, the understanding of inflammation in the skin in terms of immunology or allergology contributes to the clinical skills of dermatology. No precise definition of inflammatory skin disease is described in the text of der-

*Corresponding Author: Tetsuya Higuchi, 564-1 Shimoshizu, Sakura, Chiba 285-8741, Japan, tel: +81-43-462-8811
e-mail: higuchit@sakura.med.toho-u.ac.jp
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matology. Although we review several themes concerning immunity or allergy in dermatology with our data, under the name of “inflammatory skin diseases.”

Autoimmune Disease

Sjögren's syndrome (SjS)

It is well recognized that patients with SjS frequently develop various cutaneous manifestations during the clinical course.¹⁾ Anti-SS-A antibody-related annular erythema, which preferentially occurs in Asian patients, is considered the most important cutaneous manifestation because of its specificity.²⁾ We reported four cases of Sjögren's syndrome (SjS) who manifested a new type of annular erythema that differs from the previously described annular erythema observed in anti-SS-A/SS-B antibody positive SjS in both clinical and histological findings.³⁾ Characteristic histological features were the presence of spongiotic changes around the acrosyringium and perivascular lymphocytic infiltration without liquefaction degeneration or epidermal change, suggesting lupus erythematosus. No complement or immunoglobulin depositions were demonstrated along the basement membrane zone or around blood vessels. Clinically, this type of erythema usually appears on the trunk or extremities with itchy sensations, especially in summer, which contrasts with the preferential occurrence of the previously reported SjS-related annular erythema on the facial skin in winter. Immunologically, all four cases lacked anti-SS-A and anti-SS-B antibodies but possessed positive antimicrosome antibodies or antithyroglobulin antibodies. In three cases, metal allergy was demonstrated by a patch test, which suggests that the sweat duct is the primary target of excreted metals in this condition and that underlying SjS plays some roles in the higher prevalence of metal allergy or in the induction of sweat duct injury, similar to interstitial nephritis, which is now thought to be an exocrine manifestation of SjS.

Systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune disease manifesting inflammatory damage in a variety of organs, including glomerulonephritis.⁴⁾ The etiology of SLE involves both genetic and environmental factors, although the details are largely unknown. This disease is characterized by the production of autoantibodies to various nuclear components.⁴⁾

CD40 is a member of the tumor necrosis factor receptor family and is expressed in cells such as B cells, mac-

rophages, and dendritic cells. Its ligand, CD40 ligand (CD40L), is a member of the TNF ligand family, expressed mainly on activated T cells. CD40/CD40L plays a pivotal role in cell activation. In B cells, interaction with CD40L promotes proliferation and survival of B cells, Ig isotype switching, and germinal center reaction.⁵⁾ CD40L is ectopically expressed on B cells in patients with SLE⁶⁾ and lupus-prone BXSB mice.⁷⁾

To assess the role of ectopic CD40L expression in the development of SLE, we have established transgenic mice expressing CD40L on B cells.⁸⁾ Some of the 12-14-month-old CD40L-transgenic mice spontaneously produced autoantibodies such as antinuclear Abs, anti-DNA Abs, and antihistone Abs. Moreover, approximately half of the transgenic mice developed glomerulonephritis with immune-complex deposition, whereas the kidneys of the normal littermates showed either no pathological findings or only mild histological changes. These results indicate that CD40L on B cells causes lupus-like disease in the presence of yet unknown environmental factors that, by themselves, do not induce the disease. Thus, ectopic CD40L expression on B cells may play a crucial role in the development of SLE.

Recently, two biologic therapies, belimumab (an antibody specific to soluble B lymphocyte stimulators) and anifrolumab (an antibody specific to the type I IFN receptor subunit 1 antibiologic therapies), have been utilized to treat patients with SLE.⁹⁾ Interest in CD40-CD40L interactions in the pathogenesis of SLE and the potential to therapeutically target this interaction have been reignited in the past few years. Unfortunately, initial clinical studies of anti-CD40L mAbs were not promising.¹⁰⁾ Ruplizumab, a humanized anti-CD40L antibody, produced a partial therapeutic response in patients with lupus nephritis, resulting in an increased incidence of thrombosis in patients receiving ruplizumab. Dapirolizumab pegol, a polyethylene glycol-conjugated anti-CD40L Fab fragment, has been designed to circumvent platelet aggregation and activation and showed no evidence of prothrombotic effects in preclinical studies.¹¹⁾

Drug Eruption

To determine the causes of drug eruptions, detailed medical interviews, patch tests, and the lymphocyte transformation test (LTT) or provocation tests have been used. Since the pathogenesis of drug eruptions mainly involves T cells, which maintain long-lasting reac-

tivity to the causative drug,^{12, 13)} an *in vitro* test such as the LTT should be useful for diagnosis. We utilized CD40L as an early-activated T-cell marker. Alas, CD40L is difficult to detect because of its immediate degradation via interaction with CD40 on antigen-presenting cells.¹⁴⁾ However, antigen-specific CD4 cells have been shown to be detectable by employing stabilizing intracellular CD40L with the secretion inhibitor Brefeldin A by flow cytometry (FCM), and this stimulatory assay can be performed in as little as 24 h.^{15, 16)} We examined this method in patients with various drug eruptions.¹⁷⁾

When we performed this method relatively soon after the appearance of eruptions, positive CD40L results were obtained, compared with six patients with negative results (mean 7.1 days and 20 days, respectively). These results are consistent with those of a previous report, in which positive LTT reactions were obtained when the test was performed within one week after the onset.¹⁸⁾

In the bloodstream of patients with drug eruptions, numerous T cells with heterogeneous T-cell receptors react with the causative drug, according to the “p-I concept (pharmacological interaction with immune receptors concept)”.¹⁹⁾ Several assays to detect drug-specific T cells employing FCM are currently in use and have been described in the literature.²⁰⁻²²⁾ CD69 is one of the specific markers for T-cell activation other than CD40L, and upregulation of this surface-specific marker was reportedly detected after 48 h in LTT-positive patients.²⁰⁾ With our system, CD40L upregulation was detected in two-thirds of patients who were confirmed to have drug eruptions, and the diagnosis was made within approximately 24 h by employing intracellular FCM detection. According to the previous reports, antigen-induced CD40L reached a peak 6 h after stimulation and maintained a plateau level up to 24 h.^{15, 16)} Therefore, we performed the assay 6-24 h after stimulation, and results were obtained the next day after blood sampling. The advantages of the detection of activated markers of T cells by FCM are thought to be a shortening of the assay time and no requirement for radioactive materials. Thus, in addition to conventional drug tests, the detection of T-cell activation markers is suggested to be a useful tool for determining the causative drug in cases of drug eruptions.

Psoriasis

Psoriasis is considered not only a chronic inflammatory

skin disease but also a systemic disease. Numerous reports have shown that psoriasis is associated with obesity.²³⁾ Obesity is correlated with the severity of psoriasis.²⁴⁾ Obese psoriasis patients are often more difficult to treat. Furthermore, a dietary intervention associated with increased physical exercise and weight loss in obese psoriasis patients reduces psoriasis severity.²⁵⁾ Leptin is an adipocyte-derived hormone discovered in 1994 (Gene ID: 3952). Leptin is associated with a variety of biological effects on energy homeostasis, immune responses, wound healing, insulin resistance, and atherosclerosis.²⁶⁾ Serum leptin levels are elevated in obese subjects.²⁶⁾ Serum leptin levels show a positive correlation with the percentage of body fat and body mass index (BMI).^{26, 27)} Expression levels of leptin messenger RNA (mRNA) are significantly higher in subcutaneous adipose tissue (SAT) than in visceral adipose tissue, for both lean and obese subjects.²⁸⁾ It has been shown that leptin may play an important role in the pathogenesis of psoriasis.^{29, 31)} However, few reports are available on the association between serum leptin levels and leptin gene expression in the SAT of psoriasis patients. To clarify this point, we examined serum leptin levels and leptin mRNA expression levels in the SAT of psoriasis patients with and without obesity.³²⁾

Seventeen psoriasis vulgaris patients and six nonobese control patients who underwent skin surgery were enrolled in this study. We measured serum leptin levels. SAT samples in psoriasis patients were taken from beneath the lesional psoriatic skin at the time of skin biopsy. Leptin mRNA expression in SAT was measured using quantitative real-time reverse transcription polymerase chain reaction (real-time RT-PCR) amplification. Leptin mRNA expression showed a positive correlation with serum leptin levels and BMI. We classified psoriasis patients into two groups according to BMI: the group of nonobese psoriasis patients (BMI < 25, n=7) and the group of obese psoriasis patients (BMI ≥ 25, n=10). PASI score, serum leptin levels, and leptin mRNA expression in SAT were significantly higher in the obese psoriasis patients than in the nonobese psoriasis patients. Leptin mRNA expression in SAT was correlated with circulating levels of leptin, the severity of psoriasis, and obesity in psoriasis patients. Serum leptin levels and leptin mRNA expression levels in the SAT of nonobese psoriasis patients were not significantly different from those of nonobese controls. The altered secretion of leptin by

SAT may be related to the severity of psoriasis.

Our findings and the articles mentioned above suggest that obesity increases leptin production by SAT. The elevation of serum leptin is largely due to increased leptin production by SAT in obese psoriasis patients. Leptin affects the immune system and epidermis. Consequently, obesity could lead to the worsening of psoriasis. In summary, leptin gene expression in SAT was involved in circulating leptin levels, the severity of psoriasis, and obesity in psoriasis patients. We assume that the altered leptin secretion from SAT might be related to the worsening of psoriasis severity in obese psoriasis patients.

Dermadrome

“Dermadrome” is a coined term with a mixture of “dermatology” and “syndrome.” However, the term is almost limitedly exclusively used by Japanese dermatologists,³³⁾ and few publications with the term are cited in medical databases such as PubMed. Diagnosis and treatment of skin diseases are frequently collaborated with specialized physician. Specialized physicians frequently collaborate to diagnose and treat skin diseases. Especially, inflammatory bowel disease (IBD), representative of ulcerative colitis and Crohn’s disease (CD), exhibits various skin eruptions as an extra intestinal manifestation.^{34, 35)}

Pyoderma gangrenosum (PG), which most frequently affects the lower extremity, is a complicated disease state that results from a combination of inflammation, neutrophilic invasion, and genetic predisposition. PG is one of the most common skin manifestations of IBD and tends to arise with the exacerbation of bowel symptoms.³⁵⁾ In Japan, major systemic diseases, including IBD, were surveyed in university hospitals (including Toho University Sakura Medical Center), branch hospitals, and other main hospitals.³⁶⁾

The pathophysiology of PG is not well understood, but PG is generally considered an autoinflammatory disorder via T cells and various cytokines.³⁷⁾ For the treatment of PG, underlying diseases such as IBD should be re-evaluated and treated properly. In moderate, severe, or progressing PG, systemic treatment with oral corticosteroids, immunosuppressants, or biologics (anti-TNF preparations) is administered.³⁷⁾ Peristomal pyoderma gangrenosum (PPG) occurring around the stoma is an unusual subtype of PG and is estimated to represent 15% of PG.³⁸⁾ Once PPG occurs on the peristomal

skin, management of the ostomy appliance becomes difficult.³⁹⁾ Therefore, the collaboration of dermatologists and certified Wound Ostomy Continence nurses is important in the treatment of PPG. We encountered three cases of PPG in patients with CD that were successfully managed with appropriate ostomy care and dermatological care based on the assessment of ulcer status.⁴⁰⁾

Approach to Regulate Immune Response

To treat inflammatory skin disease, steroids, immunosuppressants, biologics, and small-molecule kinase inhibitors have been developed and clinically administered to suppress immune response. On the contrary, opposite procedures such as vaccination or immunostimulant have also been utilized to suppress immune-mediated disease. In this section, we discuss basic research and how the approach may have future clinical benefits for inflammatory skin diseases.

Several classes of antigen-loaded particles have been demonstrated to passively target antigen-presenting cells (APCs), including dendritic cells (DCs), as the most potent APC population by means of unspecific endocytic internalization.⁴¹⁾ In the course of these studies, some types of particles have been demonstrated to exert immunostimulatory activity in DCs.⁴²⁾ This property may be advantageous in order to evoke an antigen-specific immune response. However, a nanoparticle platform devoid of intrinsic immunomodulatory potential might be even more feasible, as it allows to determine the polarization of the antigen-specific immune response solely by the quality of a particle-delivered adjuvant.⁴³⁾

In this regard, we opted for dextran (DEX) nanoparticles, introduced as a carrier platform for protein antigens plus immunomodulatory compounds, to elicit an antigen-specific humoral response after *in vivo* application.⁴⁴⁾ In general, dextrans constitute dextrose-derived neutral biopolymers, which due to their excellent biocompatibility have been in widespread clinical use for decades, serving as blood volume expanders and preventing thrombosis. Therefore, DEX particles may constitute an ideal platform for the development of functionalized nanocarriers. The DEX particles used in our study are based on commercially available dextran particles with an average Mw of 500 kDa. The model protein antigen ovalbumin (OVA) and lipopolysaccharide (LPS), a well-established toll-like receptor (TLR)-4 ligand and TH1-promoting DC stimulus, were adsorbed to DEX particles

by applying the protocol introduced by Schröder et al.^{44,45)}

It has been shown that uptake of OVA by pinocytosis in DCs resulted in the activation of OVA-specific CD4⁺ T cells, but evoked no CD8⁺ T-cell response.⁴⁶⁾ In contrast, endocytic uptake of OVA, which is efficiently bound by the mannose receptor (MR) due to its mannosylation,⁴⁷⁾ resulted in strong activation of either T-cell population. The MR belongs to a group of C-type lectin receptors that act as pattern recognition receptors and bind both endogenous and pathogen-derived structures.⁴⁸⁾ Due to its rather restricted expression pattern, largely confined to macrophages and myeloid DC populations, the MR has become a well-established target receptor for APC-specific vaccination.⁴⁹⁾

In our study, we analyzed the efficacy of a refined MR-targeting delivery system based on OVA, intended to serve both as a MR-targeting molecule and as a source of antigen.⁵⁰⁾ We show that DEX-based nanoparticles are not internalized by DCs and lack unwanted immunomodulatory function. DEX particles adsorbed with OVA, however, were efficiently engulfed by murine DCs *in vitro* in a MR-dependent manner. Codelivery of OVA and LPS by DEX particles induced stronger and more sustained immune responses *in vitro* and *in vivo* than direct application of these compounds, which confirms their usability for immunotherapeutic applications.

Conclusion

We reviewed our clinical and experimental research data and cited associated references for each subject. From the physical view of the dermatologist, a visible skin eruption implies various immune responses in the skin and understanding the underlying mechanisms leads to precise diagnosis and effective treatment. Consecutive experimental research is expected to find the etiology of the disease and the development of new diagnostic and therapeutic materials/methods.

Conflicts of interest: None declared.

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Tetsuya Higuchi**Education**

- 1988-1994 School of Medicine, Tokyo Medical and Dental University
1997-2001 Graduate School of Medicine, Tokyo Medical and Dental University

Professional Experience

- 1995 Department of Dermatology, Chigasaki Tokushukai Hospital
1996 Department of Dermatology, Tsuchiura Kyodo Hospital
2001-2003 Assistant Professor, Department of Dermatology, Tokyo Medical and Dental University
2003-2005 Research Fellow, Department of Dermatology, University of Münster, Germany
2005-2008 Lecturer, Department of Dermatology, Tokyo Medical and Dental University
2008-2017 Associate Professor, Department of Dermatology, Toho University Sakura Medical Center
2017-present Professor, Department of Dermatology, Toho University Sakura Medical Center
-