e-ISSN 3050-8460
Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Coexistence of Allergic Contact Dermatitis and Immediate-Type Hypersensitivity Reactions, Two Contrasting Immunological Responses: A Literature Review

Mancuso Giuseppe[1*]

[1]Occupational Medicine Center, Ravenna, Italy

***Correspondence author:** Mancuso Giuseppe, MD, Occupational Medicine Center, Ravenna, Italy; Email: g.mancuso50@gmail.com

Citation: Giuseppe M. Coexistence of Allergic Contact Dermatitis and Immediate-Type Hypersensitivity Reactions, Two Contrasting Immunological Responses: A Literature Review. J Dermatol Res. 2025;6(3):1-6.

https://doi.org/10.46889/JDR.2025.6315

Received Date: 11-11-2025

Accepted Date: 26-11-2025

Published Date: 04-12-2025

Abstract

Despite the mutual inhibitory properties of CD4 (Cluster of Differentiation)+Th1 (T helper) and Th2 cells, it has been reported that allergic contact dermatitis and immediate-type hypersensitivity reactions (mainly regulated by CD4+Th1 and CD4+Th2 cells, respectively) can coexist. The association can affect a single organ or multiple distinct organs, often through different effector mechanisms and can be induced by two or more allergens or by a single allergen. Actually, little is known about how these two types of reactions interact and mutually reshape the immune response. Their coexistence may suggest that regulatory mechanisms through mutual inhibition of CD4+ T cell phenotypes are not operative. Furthermore, mechanisms operating outside the classic Th1/Th2 paradigm, represented primarily by regulatory Treg cells and their anti-inflammatory cytokines, do not appear to have effective inhibitory activity on either allergic reaction. In order to detect the possible presence of both hypersensitivities, a careful clinical/anamnestic evaluation would be appropriate for each dermatological patient. Cutaneous and extracutaneous manifestations attributable to one of the two types of hypersensitivity may be absent at the time of the visit and detectable only as anamnestic data.

Keywords: Allergic Diseases; Delayed-Type Hypersensitivity; Allergic Contact Dermatitis; Immediate-Type Hypersensitivity; TH1/TH2; Cytokines

Introduction

Immediate allergic reactions and Allergic Contact Dermatitis (ACD) represent two theoretically contrasting types of hypersensitivity. ACD (type IV hypersensitivity) is a delayed cell-mediated allergic response in which CD4+ Th1 (a subset of CD4+ helper T cells) and CD8+ T lymphocytes act as the main effectors [1]. CD4+ Th1 lymphocytes produce pro-inflammatory cytokines such as IFN-γ (Interferon-gamma) and tumor necrosis factor. In particular, the cytokine IFN-γ inhibits the differentiation of CD4+ Th2 cells (a subset of CD4+ helper T cells) and promotes inflammatory pathways primarily through macrophage activation. More recently, the important role of CD4+ Th17 cells in the release of inflammatory cytokines such as IL-17 has also been recognised [1-3]. The immediate allergic reaction (type I hypersensitivity) is a humoral response (present in atopic conditions such as urticaria, allergic rhinitis and asthma) orchestrated by CD4+Th2 lymphocytes mainly through related cytokines including IL-4, IL- 5, IL- 6, IL- 9, IL- 10 and IL- 13. IL-4 and IL-13 are the main Th2 cytokines that drive CD4+Th2 responses, suppress Th1/Th17 differentiation and stimulate B-cell differentiation/IgE production and eosinophil growth and recruitment [2].

Materials and Methods

A literature review was conducted using PubMed and Google Scholar databases to evaluate the association between immediate allergy and ACD in the same individual. We focused our attention on the ways in which the two contrasting reactions interact and reshape the immune response and on the mechanisms that favour their coexistence We used a standardized search approach using Boolean search terms "AND" or "OR" The search included a combination of terms: coexistence, allergic contact dermatitis, immediate allergy, Th1 and Th2 balance, regulatory T cells, Foxp3, TGF-β and hapten-specific polarization. Following this research, 35 articles were selected and cited in this work. These included 20 case reports, 2 retrospective and 2 prospective

epidemiological studies, 5 literature reviews and 6 clinical-immunological studies. No limits of publication date were observed.

Allergens Responsible for Concomitant Immediate Allergy and ACD

The association can involve a single organ or several distinct organs, often through different effector mechanisms and can be induced by a single allergen or by two or more allergens [4,5]. Different types of allergens can lead to different comorbidities. In the study by Tsui, et al., patients with occupational asthma exposed to low molecular weight agents such as metals, fragrances and epoxy resins, had a higher risk of previous or concomitant ACD and a lower risk of rhinitis than those exposed to high molecular weight agents such as glycoproteins of plant, animal or microbiological origin [6]. In the study by Amornruk, et al., 40 patients who had ACD to fragrances documented by positive standard patch tests were retested with 28 different fragrance components; the tests showed concomitant immediate and delayed patch test reactions, the most frequent association being that induced by cinnamic aldehyde (8/40 cases) and cinnamic alcohol (6/40 cases) [7]. Sneezing and runny nose were the two most common symptoms related to immediate patch test reactions. However, in many other cases, immediate reactions to fragrances have been interpreted as non-immunological in nature and therefore induced through mechanisms completely separate from those of delayed allergic reactions possibly associated [8].

Two patients who suffered from occupational immediate allergy (asthma) with concomitant ACD both induced by epoxy resins based on diglycidyl ether of bisphenol A (a stabilizing component) were reported by Kanerva, et al., [9]. In one of the two patients, there was also an immediate allergy to Methyltetrahydrophthalic Anhydride (MTHPA) and Methylhexahydrophthalic Anhydride (MHHPA) (two phthalic anhydrides used as hardeners for epoxy resins) documented by a positive prick test and IgE determination. MHHPA has been reported to cause contact allergic urticaria and rhinitis and associated ACD [10].

Coexistence of immediate allergic reactions and ACD, both induced by Natural Rubber Latex (NRL), has been reported [11,12]. However, the importance of NRL as a type IV allergen is unclear. According to some authors, NRL patch test reactions are in many cases irritative in nature or due to a concomitant allergy to NRL additives [13].

As shown by some population-based studies and case reports, nickel (as a single allergen or in conjunction with other allergens) seems to be responsible for the association of the two polar types of reaction [4,5,14]. The study by Kolberg, et al., showed that self-reported contact allergy to nickel is associated with wheezing in young males and females and exclusively with asthma in males [14]. In contrast, no significant association was observed in either sex for incident rhinoconjunctivitis. According to the authors, it remains to be clarified whether the association is due to environmental or genetic predisposition or to an overlap of the mechanisms of type I and type IV hypersensitivity. Corroborating this last eventuality is the case described by Estlander, et al., concerning a metal grinding worker in whom nickel induced ACD, allergic contact urticaria, rhinitis and asthma. Scratch chamber tests, open tests, specific IgE determinations Radioallergosorbent Test (RAST) and RAST-inhibition test confirmed that the patient had developed an IgE-mediated allergy to nickel, although with a late response to bronchial provocation test with NiSO4; positive patch tests to nickel confirmed the concomitant ACD [4].

A review of the literature shows that many other agents can produce combined ACD and immediate hypersensitivity reactions. Among these agents, the presence of allergens belonging to acrylates, drugs, dyes, plant, antiseptics and preservatives has been reported [15,17-29].

Blood Inflammatory Markers in Patients Presenting the Two Polar Types of Hypersensitivity

Two studies on blood inflammatory markers in patients presenting the two polar types of hypersensitivity provide interesting data on how these interact and reciprocally reshape the immune response. In the study by de Mello, et al, patients presenting the two contrasting types of hypersensitivity-immediate (asthma and/or rhinitis) to mites (Derp) and delayed (ACD) to nickel (Derp+Ni group), were analyzed for cytokine production in serum and in cell culture supernatants after mitogens such as Phytohemagglutinin (PHA) and/or specific antigen stimulation [5]. The results were compared with those collected in a group of patients allergic exclusively to nickel (Ni group), to mites (Derp group) and in non-sensitized subjects (negative group). After PHA stimulation, IFN-γ levels in the culture supernatants were lower in the Derp+Ni group than in the Ni group. This result could suggest an inhibitory mechanism exerted *in-vitro* by the Th2 response on the Th1 response, an inhibition which however is not clinically evident. According to the authors' hypothesis, the coexistence of the two contrasting types of reaction to different allergens could be due to their compartmentalization in distinct target organs, where the reciprocal inhibitory control of Th1/Th2

cells seem to be hiding. The dosage of Th2 cytokines, such as IL-5 and IL-13, showed higher levels in the culture supernatants after PHA stimulation in the Derp+Ni group compared to the negative group and the Ni group. IL-4 was largely observed on serum samples from all subjects groups and IL-13 serum levels were significantly higher in Derp group compared to Negative group . Regarding the regulatory cytokines, analysis of (Transforming Growth Factor) TGF-β production after Derp and PHA stimulation showed higher levels in the Derp+Ni group than among non-sensitized or nickel-sensitized subjects. IL-10 levels did not differ in the studied groups after stimulation with antigens or PHA, but basal production was higher in the Derp and Derp+Ni groups than in the Ni group. Furthermore, serum samples from subjects in the Derp group had higher IL-10 levels than those in the Derp + Ni group.

In the study by Chai, et al., patients with ACD to various allergens (including nickel and other metals) and Allergic Rhinitis (AR) caused by various inhalant allergens were compared to non-sensitized subjects and to patients with both types of allergy (ACD + AR) [16]. Serum levels of IgG, IgG4 (an immunosuppressive mediator for IgE-mediated anaphylaxis) and IgA were elevated in AR and ACD + AR patients but not in the ACD group. IgE were elevated in all three sensitized patient groups. Patients with AR expressed elevated levels of pro-inflammatory Th2 cytokines such as IL-4, IL-8 and IL-6, while patients with ACD + AR presented a moderate change in serum cytokines (increased expression of IL6 alone). Other cytokine serum levels including IFN-γ, IFN-α2, IL-1β, IL-1 α, IL-10, IL-12, IL-17A and TNF- α did not show significant differences in the studied groups. The ACD + AR group showed an increase in memory CD8+ T cells and a decrease in naïve CD8+ T cells (similar changes with an increase in memory CD4+ T cells and a decrease in naïve CD4+ cells were observed in the AR group). A higher incidence and a broader spectrum of autoantibodies (IgG) (as a consequence of a loss of central and/or peripheral self-tolerance) was present in the ACD + AR group compared to the AR or ACD group. It has been hypothesized that ACD + AR comorbidity represents an increased risk of autoimmune disorders [16].

Defective Regulatory Mechanisms and Other Favoring Factors

Coexistence mechanisms favoring the association have not been clarified, but they could hypothetically concern:

- a defect in regulatory mechanisms
- a shared immune polarization

Defective Regulatory Mechanisms

The coexistence of clinical signs and symptoms of both polar types of hypersensitivity could indicate that regulatory mechanisms through mutual inhibition of Th1/Th2 cellular phenotypes (according to the Th1/Th2 balance hypothesis) are not operational [5]. Mechanisms that operate outside the classic model of Th1/Th2 cross-regulation, represented mainly by regulatory T cells (Tregs) (defined by the expression of CD4, the IL-2 receptor alpha chain (CD25) and the transcription factor Foxp3), also do not appear to have effective inhibitory activity on the two Th1/Th2 reactions [5]. It is well known that Treg cells (CD4+ CD25+ Foxp3+) are important for controlling the immune response to self and foreign antigens through various mechanisms, including cytolysis of target cells following direct cell-to-cell contact and the production of anti-inflammatory cytokines, including IL-10, TGF-β1 and IL-35 (Fig. 1) [30-34]. However, suppressive efficiency of peripheral Treg cell (produced in the periphery from naive CD4+ precursor cells following antigen exposure and in the presence of TGF-β) can be inhibited by high levels of Th2 (in particular IL-4 and IL-6) and Th1 (in particular IFN-γ) cytokines according to mechanisms of negative cross-regulation not yet fully elucidated [5,33,34] . In this respect, Takaki, et al., observed that high levels of IL-4 suppress TGF-β1-induced expression of Foxp3 (essential for development and regulatory function of Tregs) by promoting the binding of STAT6 (a key transcriptional regulator) to the Foxp3 promoter silencer region [33]. It is likely that the suppressive activity of peripheral Tregs may be significantly reduced, especially in the most intense phases of the inflammatory response where the concentration of Th1/Th2 effector cytokines is highest [34]. However, it is likely that Treg cells can be re-induced in the late phase of inflammatory immune responses, when Th1/Th2 effector activity is reduced [34]. IL-4 has no effect on Foxp3 levels in naturally occurring Treg cells produced in the thymus in the absence of exogenous antigen stimulation. The above data may contribute to understanding the possible defective regulatory mechanisms underlying the coexistence of delayed and immediate-type hypersensitivity reactions. Other studies on blood inflammatory markers reported above would confirm, albeit indirectly, the involvement of these mechanisms in patients presenting with both types of allergic reactions [5,16].

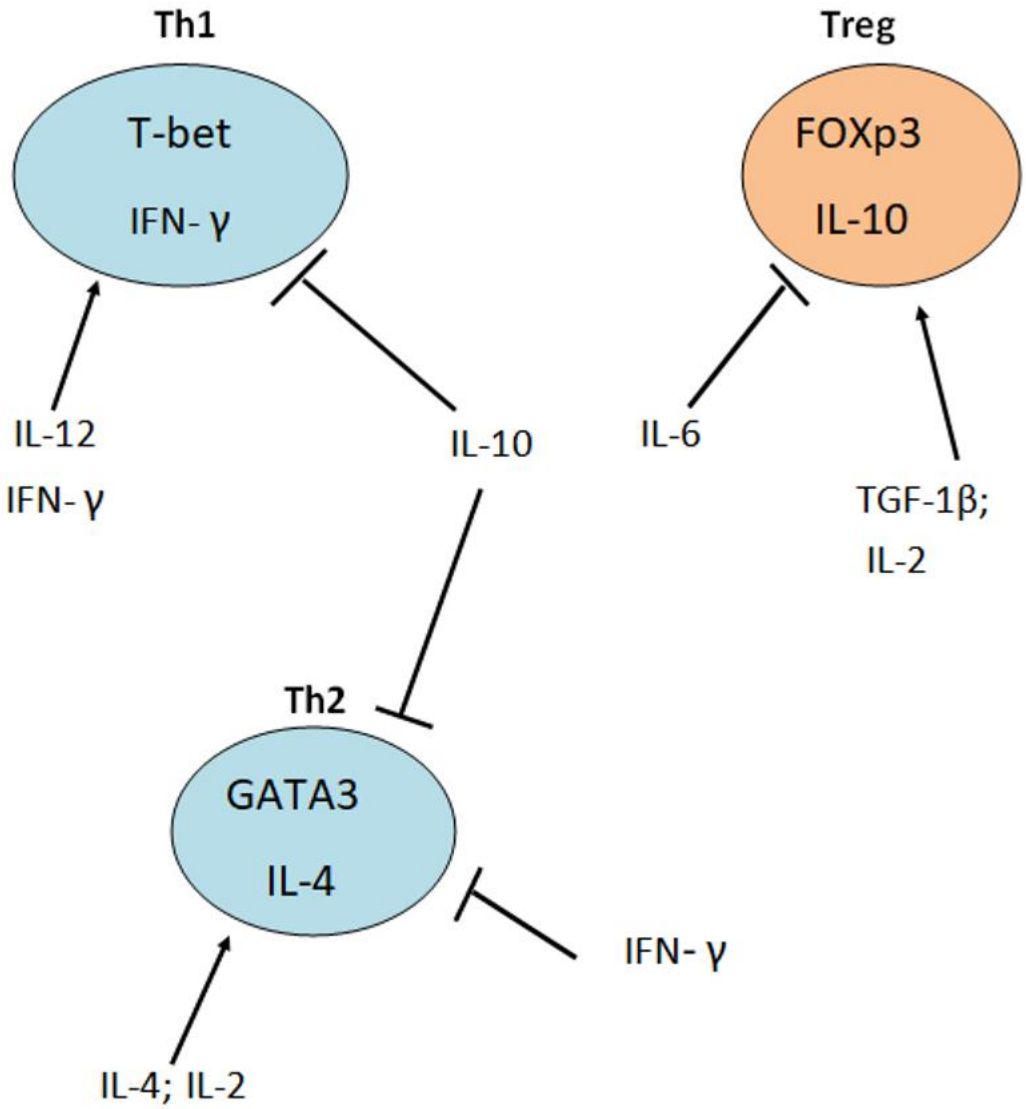

Figure 1: The diagram illustrates the Th1/Th2/Treg interaction mediated by cytokines produced by the same cell subsets, each of which has distinct transcription factors. IL-10 produced by Treg cells acts as an important inhibitory factor on the polarization and proliferation of both Th1 and Th2 cells.

A Shared Immune Polarization

The immune response in ACD should not be considered a uniform immune phenomenon. In fact, although clinical contact allergic reactions are similar in all allergen groups, different immune polarizations can characterize different allergens [35]. Contact allergens, such as fragrances, rubber and 2,4,6- trinitrochlorobenzene, induce (especially when associated with an atopic background) strong TH2 polarization and some TH22 bias, with much more modest TH1/TH17 contributions [2]. In these cases, the shift toward a predominantly CD4 + Th 2 immune response could contribute to favoring the association of ACD with possible immediate CD4 + Th2 allergic reactions.

However, the involvement of such a mechanism in favoring the coexistence of the two types of clinically distinct reactions is only hypothetical, as there is no confirmatory data in the literature regarding its actual importance.

Conclusion

Several causal factors could favor the coexistence of immediate and delayed allergic reactions. Among these factors, defective regulatory mechanisms are a possible cause, but the immunological processes involved remain to be fully elucidated. From a clinical point of view, it is important to be aware of the possible coexistence of two distinct types of hypersensitivity reactions,

the identification of which requires careful clinical/anamnestic investigation for each dermatological patient. It should be noted that cutaneous and/or extracutaneous manifestations attributable to either type of hypersensitivity may be absent at the time of examination and detectable only by a thorough medical history. Confirmed coexistence requires further and more in-depth allergy testing.

Conflicts of Interest

The authors declare no conflict of interest in this paper.

Funding

None

Authors' Contributions

Author contributed to conceptualization, treatment execution, manuscript writing and final approval.

References

1. Rustemayer T. Immunological mechanisms in allergic contact dermatitis. Curr Treat Options Allergy. 2022;9:67-75.
2. Belmesk L, Muntyanu A, Cantin E, AlHalees Z, Jack CS, Le M, et al. Prominent role of type 2 immunity in skin diseases: beyond atopic dermatitis. J Cutan Med Surg. 2022;26:33-49.
3. Masahiro S. Role of T helper 17 cells in allergic contact dermatitis: role of Th17 cells in ACD. J Dermatol Res. 2020;5:191-7.
4. Estlander T, Kanerva L, Tupasela O, Keskinen H, Jolanki R. Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. Clin Exp Allergy. 1993;23:306-10.
5. De Mello LM, Bechara MI, Sole D, Rodrigues V. TH1/TH2 balance in concomitant immediate and delayed-type hypersensitivity diseases. Immunol Lett. 2009;124:88-94.
6. Tsui HC, Ronsmans S, Hoet PHM, Nemery B, Vanoirbeek JAJ. Occupational asthma caused by low-molecular-weight chemicals associated with contact dermatitis: a retrospective study. J Allergy Clin Immunol Pract. 2022;10:2346-54.
7. Amornruk N, Siranart N, Sittiwattanawong P, Kueanjinda P, Loplumlert S, Wongpiyabovorn J. Immediate patch test reaction to fragrance in patients with allergic contact dermatitis to fragrance: A prospective study. J Am Acad Dermatol. 2022;87:1042-8.
8. Tanaka S, Matsumoto Y, Dlova N, Ostlere LS, Goldsmith PC, Rycroft RJ, et al. Immediate contact reactions to fragrance mix constituents and Myroxylon pereirae resin. Contact Dermatitis. 2004;51:20-1.
9. Kanerva L, Jolanki R, Tupasela O, Halmepuro L, Keskinen H, Estlander T, et al. Immediate and delayed allergy from epoxy resins based on diglycidyl ether of bisphenol A. Scand J Work Environ Health. 1991;17:208-15.
10. Kanerva L, Hyry H, Jolanki R, Hytönen M, Estlander T. Delayed and immediate allergy caused by methylhexahydrophthalic anhydride. Contact Dermatitis. 1997;36:34-8.
11. Placucci F, Vincenzi C, Ghedini G, Piana G, Tosti A. Coexistence of type I and type IV allergy to rubber latex. Contact Dermatitis. 1996;34:76.
12. Sommer S, Wilkinson SM, Beck MH, English JS, Gawkrodger DJ, Green C. Type IV hypersensitivity reactions to natural rubber latex: results of a multicentre study. Br J Dermatol. 2002;146:114-7.
13. Wakelin SH, Jenkins RE, Rycroft RJ, McFadden JP, White IR. Patch testing with natural rubber latex. Contact Dermatitis. 1999;40:89-93.
14. Kolberg L, Forster F, Gerlich J, Weinmayr G, Genuneit J, Windstetter D, et al. Nickel allergy is associated with wheezing and asthma in young German adults: Results from the SOLAR study. ERJ Open Res. 2020;6:00178-2019.
15. Lindström M, Alanko K, Keskinen H, Kanerva L. Dentist's occupational asthma, rhinoconjunctivitis and allergic contact dermatitis from methacrylates. Allergy. 2002;57:543-5.
16. Chai W, Zhang X, Lin M, Chen Z, Wang X, Wang C, et al. Allergic rhinitis, allergic contact dermatitis and disease comorbidity belong to separate entities with distinct composition of T-cell subsets, cytokines, immunoglobulins and autoantibodies. Allergy Asthma Clin Immunol. 2022;18:10.
17. Mancuso G. Immediate and delayed contact hypersensitivity to thiocolchicoside. Acta Dermatovenerol Alp Pannonica Adriat. 2018;27:203-5.
18. Jovanović M, Karadaglić D, Brkić S. Contact urticaria and allergic contact dermatitis to lidocaine in a patient sensitive to benzocaine and propolis. Contact Dermatitis. 2006;54:124-6.

19. Isaksson M, Bruze M, Hörnblad Y, Svenonius E, Wihl JA. Contact allergy to corticosteroids in asthma/rhinitis patients. Contact Dermatitis. 1999;40:327-8.
20. Iwata JI, Inomata N, Sato M, Miyakawa M, Kawaguchi T, Aihara M. Contact dermatitis with concomitant contact urticaria syndrome due to multiple ingredients of oxidative hair dye. Allergol Int. 2019;68:114-6.
21. Potter PC, Mather S, Lockey P, Knottenbelt JD, Paulsen E, Skov PS, et al. Immediate and delayed contact hypersensitivity to verbena plants. Contact Dermatitis. 1995;33:343-6.
22. Krook G. Occupational dermatitis from Lactuca sativa (lettuce) and Cichorium (endive): simultaneous occurrence of immediate and delayed allergy. Contact Dermatitis. 1977;1:27-36.
23. Lakshmi C, Srinivas C. Parthenium the terminator: An update. Indian Dermatol Online J. 2012;3:89-100.
24. Tanaka T, Moriwaki SI, Horio T. Occupational dermatitis with simultaneous immediate and delayed allergy to chrysanthemum. Contact Dermatitis. 1987;16:152-4.
25. Madsen MT, Andersen F, Paulsen E. Concomitant immediate and delayed sensitization by philodendron (Philodendron scandens) in a plant keeper. Contact Dermatitis. 2017;77:326-8.
26. Paulsen E, Hvid L, Andersen F. Immediate and delayed contact reactions to white and green tea blends. Contact Dermatitis. 2022;86:134-6.
27. Treudler R, Tebbe B, Orfanos CE. Coexistence of type I and type IV sensitization in occupational coffee allergy. Contact Dermatitis. 1997;36:109.
28. Hoyos CL, Echevarría AG, Leal RP, Spröhnle JL, Imbernon DB, Finello M, et al. Immediate and delayed hypersensitivity to chlorhexidine coexisting in the same patient. Contact Dermatitis. 2024;90:320-2.
29. Gonçalo M, Gonçalo S, Moreno A. Immediate and delayed sensitivity to chlorocresol. Contact Dermatitis. 1987;17:46-7.
30. Rocamora-Reverte L, Melzer FL, Würzner R, Weinberger B. The complex role of regulatory T cells in immunity and aging. Front Immunol. 2021;27:616949.
31. Cavani A, Nasorri F, Ottaviani C, Sebastiani S, De Pità O, Girolomoni G. Human CD25+ regulatory T cells maintain immune tolerance to nickel in healthy, nonallergic individuals. J Immunol. 2003;171:5760-8.
32. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol. 2008;8:523-32.
33. Takaki H, Ichiyama K, Koga K, Chinen T, Takaesu G, Sugiyama Y, et al. STAT6 inhibits TGF-β1–mediated Foxp3 induction through direct binding to the Foxp3 promoter, reversed by retinoic acid receptor. J Biol Chem. 2008;283:14955-62.
34. Wei J, Duramad O, Perng OA, Reiner SL, Liu YJ, Qin FX. Antagonistic nature of T helper 1/2 developmental programs in opposing peripheral induction of Foxp3+ regulatory T cells. Proc Natl Acad Sci U S A. 2007;104:18169-74.
35. Dhingra N, Shemer A, Correa da Rosa J, Rozenblit M, Fuentes-Duculan J, Gittler JK, et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. J Allergy Clin Immunol. 2014;134:362-72.