Immunological Aspect of Atopic Dermatitis

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Abstract: Because atopic dermatitis (AD) is considered to be caused by a wide range of factors, it cannot be attributed to a single etiology. Many theories that have been advanced appear to contradict clinical findings. For example, the hypothesis that Th-2 cells are primarily responsible for the pathology of AD has become questionable because IFN-γ is not effective and because Th-1 cells have also been shown to be important for the pathogenesis. The hypothesis that T cells infiltrating the skin lesion express high levels of cutaneous lymphocyte antigen (CLA), which functions as a skin homing receptor for T lymphocytes, leading to the exacerbation of erythema AD lesions, has rapidly lost support, because it has been shown that CLA itself is not the direct ligand for E-selectins. Similarly, the hypothesis that the exacerbation of AD symptoms of bacterial infections, which can be attributable to bacterial superantigens, has been refuted, because T cells in AD patients have been shown to be less sensitive to superantigens. Therefore, a thorough analysis of data from studies in animal models would be more beneficial in providing clues regarding the pathology of AD than the direct extrapolation of in vitro findings.

Key words: Th-1/Th-2 cytokine; CLA; Fuc-T VII; Superantigen

Introduction

There is continuing controversy as to whether atopic dermatitis can be attributed to an immunological disorder or a disorder of abnormal barrier functions. However, neither scenario is mutually exclusive, because in general the cause for disease development is usually multifactorial. Even for infectious diseases where the cause may appear to be unifactorial, various in vivo factors are involved in the process from viral invasion to manifestation of the disease.

Therefore, given a variety of clinical conditions associated with atopic dermatitis (AD), it would be logical to presume that the causes of AD are multifactorial.

Th1/Th2 balance in AD

Since Mosmann et al.1) reported in 1986 that T cells can be divided into Th-1 and Th-2 according to the patterns of cytokines produced by CD4+ T cells in mice, an increasing number of researchers have tried to explain the patho-
genesis of many inflammatory diseases solely based on the Th-1/Th-2 balance. It has been postulated that AD is mediated by Th-2 cells based on findings, such as elevated IgE levels and eosinophilia.

Kapsenberg et al.\(^2\) reported that Dp specific T-cell clones, established from the peripheral blood mononuclear cells (PBMCs) of AD patients, produced Th-2 cytokines, such as IL-4 and 5, while tetanus-toxin or Candida specific T-cell clones derived from the same patients produced IFN-\(\gamma\), but no IL-4 and 5. Parronchi et al.\(^3\) also reported the predominance of Dp-specific Th2 cells in AD lesions, suggesting the possibility that Dp-specific Th2 cells play a key role in the pathogenesis of AD.

In addition, van der Heijden et al.\(^4\) analyzed T-cell clones derived from AD lesions and showed that the frequency of Dp-specific T clones were significantly higher in the skin lesions than that of the corresponding T-cell clones in PBMCs of the same patients, and that most of those were of Th-2 phenotype that can produce IL-4 but not IFN-\(\gamma\). These results strongly indicate that Th-2 cells are primarily responsible for the development of AD lesions.

However, there have been conflicting data reported. For example, it was reported that the levels of IFN-\(\gamma\)-mRNA expression in AD lesions were higher than in contact dermatitis (CD) thought to be caused by Th-1, and that the levels decreased upon resolution.\(^5\) In addition, the therapeutic effect of IFN-\(\gamma\) on AD has not been achieved to the expected levels.\(^5\) Thus, it remains to be established whether or not AD is a Th-2-mediated disease. In this regard, Grewe et al.\(^5\) provided an alternate explanation by assuming that acute lesions are mediated by Th-2 cells, while chronic lesions are mediated by Th-1 cells. These results indicate that caution is needed in making the assumption that Th-2 cells are primarily involved in the pathogenesis of AD. The involvement of Th1 cells, therefore, should also be considered, while the relative balance is shifted toward Th2. Thus, the most likely scenario is that the interplay between Th1 and Th2 cells is important for the development of atopic dermatitis.

CLA Expression on T Cells of AD Patients

The cutaneous lymphocyte-associated antigen (CLA) is reported to be a carbohydrate antigen that is preferentially expressed on skin-homing T cells. Its ligand is considered to be E-selectins whose expression is preferentially induced on vascular endothelial cells of the skin. A dogma has been established that CLA\(^+\) T cells migrate to the skin by adhering to E-selectins on vascular endothelial cells in the skin. Babi et al.\(^6\) showed that T cell proliferation activity in response to mite antigens is independent of CLA expression in T cells from asthma patients, while positive for CLA\(^+\) T and weak for CLA\(^-\) T cells in PBMCs from AD patients only with dermatitis.

Besides, Abernathy-Carver et al.\(^7\) showed a significant increase in the number of CLA\(^+\) T cells in milk-sensitive AD patients as compared to milk-sensitive patients with enteritis. These results were interpreted as suggesting that T cells of AD patients express CLA in response to such allergic stimulations like those with mite antigens and infiltrate into the skin, resulting in the exacerbation of the skin lesion. We also showed that most of the increased Th-2 cells producing IL-4 and IL-13 in PBMCs of AD patients were CLA positive, and that Th-1 and Tc-1 cells producing IFN-\(\gamma\) were frequently observed in CLA\(^-\) fractions.\(^8\)

These results have been considered as evidence for the importance of CLA in the skin-homing of T cells, since a significant increase in CLA\(^+\) T cell number observed in PBMCs of AD patients seemed to support this notion. However, this notion should be re-examined based on newly discovered data and the following experimental findings.

First, it becomes clear that CLA itself is not a ligand of E-selectin. It has been shown that CLA expression is controlled by a kind
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of glycosyltransferase, fucosyltransferase VII (FucT VII), which induces a binding site for E-selectin. In other words, CLA is mere a carbohydrate epitope whose expression is induced together with the ligand of E-selectin by Fuc-T VII (Fig. 1).

Second, in most cases, antigen stimulation of CLA T cells results in the down regulation of the CLA expression in the early stage (even if the ligand of E-selectin increases), and rather, the CLA expression is induced later with the cessation of proliferation. That means when naive CD4+ T cells that are destined to differentiate into mite-specific T cells are stimulated by Dp antigens, CLA expression is not immediately induced even if they differentiate into effector/memory T cells.

There are other problems with the role of CLA. On the contrary to our initial expectation, expression of CLA on T cells in the blood increases after the resolution of skin inflammation. We have shown that the expression of Fuc-T VII mRNA is downregulated by IL-4, and upregulated by IL-12.10 The question then arises why CLA+ T cells increase in number in PBMC of AD patients with increased IL-4 production? This is a perplexing and paradoxical finding. To resolve this issue, we developed a mAb that can detect the expression of Fuc-T VII at the protein level, and investigated CLA+ T cells in PBMCs using this mAb.

This mAb can identify a distinct subset of CD4+ and CD8+ T cells in PBMCs that can be divided into 3 phenotypes, Fuc-T VII+CLA+, Fuc-T VII+CLA+, and Fuc-T VII-CLA+.11 While Fuc-T VII+CLA+ cells are the most abundantly identifiable phenotype in healthy individuals, Fuc-T VII-CLA+ cells are the highest in AD patients. Considering that most Fuc-T VII+CLA+ cells are assumed to be Th-1 cells, why the CLA+ T cells increase in AD patients despite increased production of IL-4 remains the great enigma. The increase in Th-1-type skin-homing T cells in AD patients contradicts the previous dogma. This is due in part to the misconception that T cells in PBMCs reflect the true numbers of T cells existing in the body. The fact is that only about a few % of T cells are located in the blood, the remaining T cells being principally located in the spleen and lymphatic system. It should be therefore noted that an increase in the number of T cells entering the skin from the blood would be accompanied by a proportionate decrease in this type of T cells in the blood, assuming that a constant number of such T cells exist in the body.

Great caution is needed in making the assumption that the frequency of a certain T-cells subset in the blood reflects the true numbers of all T cells in the body. Evidence for this includes the finding that T cells, which can otherwise migrate into the skin, accumulate in the blood in E-selectin and P-selectin-knock out mice.

A growing amount of new data challenges a dogma postulating that Th-2 cells dominate and CLA+ skin-homing T cells increase in AD. However, further discussion thoroughly examining these notions is warranted.

Roles of Superantigens in AD

It is widely accepted that bacteria, such as Staphylococcus aureus detected in lesions, cause exacerbation of AD. A logical consideration would be that superantigens derived form bacteria exacerbate skin lesions. Superantigens
include toxins derived from bacteria that can activate T cells regardless of TCR-Vδ gene usage, by directly binding both to MHC class II antigens on antigen-presenting cells and the TCR-Vβ chain of T cells. Therefore, if superantigens activate T cells in AD patients, the Vβ repertoire of T cells infiltrating into tissues and in the blood must be specifically biased in a superantigen specific manner. Unfortunately, however, the existence of such a bias has not been observed.

It should be noted that an initial in vivo administration of superantigens would cause the proliferation of T cells specific to certain Vβ but the following would result in anergy specific to the Vβ. Therefore, this anergic state would render the host at risk for recurrent infection. In support of this notion, Tokura et al.12) showed that compared with controls the reactivity to superantigens derived from Streptococcus pyogenes and its ability to produce TNF-α were suppressed in PBMCs of AD patients with impetigo caused by Streptococcus pyogenes.

Knowledge Learned from Studies Using an Animal Model

There were many contradictory results obtained from the analysis of the lesions and PBMCs of AD patients, which cannot be explained by a single mechanism. To overcome the potential problem of these clinical studies, we have tried to establish an animal model in which a condition similar to AD could be reproduced. These results have been thoroughly presented in our previous reports,13,14) and the reader is invited to review these reports.

In brief, repeated applications of hapten to the ear of mice caused a gradual shift from a Th-1-dominated (the acute phase) to a Th-2-dominated immune response (the chronic phase). Serum IgE levels concomitantly increased significantly, and local immune responses as evidenced by swelling of the ear shifted from typical delayed hypersensitivity to immediate hypersensitivity followed by a late-phase reaction (LPR). Many of the immunological alterations observed in AD lesions can be reproduced in this model at the chronic phase. This can be regarded as an appropriate mouse model for AD.

We have been successfully establishing various types of immune responses by repeated applications of different haptens on genetically different strains of mice. The repeated application of hapten on C57BL/6, in which a Th-2 response is difficult to be induced would also induce the shift to the Th-2 reaction associated with the development of LPR; but because IgE levels did not increase, an immediate-type reaction did not develop. In fact, there are many AD cases with no increase in serum IgE levels, and this model using C57BL/6 can be used as an appropriate model for such cases.

One of the factors contributing to the pathogenesis of AD is a decrease in ceramide 1, which is one of the ceramides that are major constituents of intracellular lipids in the stratum corneum. It is theoretically possible that repeated administration of various allergens, such as hapten, to the barrier-disrupted skin results in the development of AD. According to this notion, the Th-2-dominated response characteristic for AD can be interpreted as a secondary phenomenon. In fact, in this animal model, repeated applications of hapten on the barrier-disrupted skin caused a prompt shift to Th-2, supporting the notion that barrier dysfunction in the stratum corneum is primarily responsible for the development of AD.

However, there is no definitive evidence, as yet, to indicate that alterations in ceramides occur congenitally in patients with AD irrespective of inflammation. We reason that a decrease in ceramides by repeated inflammations would allow invasion by allergens, and once repeated entry of allergens through barrier-disrupted skin has occurred, a vicious cycle leading to a Th-2-dominated responses will result.
Conclusions

Although a wide variety of studies have been performed to establish the etiology of AD, there is no convincing concept so far. It is almost impossible to explain all of the events occurring in AD by a single concept.

In the process of establishing an animal model, we have found that repeated elicitation of contact dermatitis, which was thought to be an opposite disease from AD, can reproduce AD-like symptoms. Therefore, if contact dermatitis is repeated in an unrecognized fashion, the protective or restorative reactions against this by the host would be manifested as skin lesions in AD. If so, there would be the danger of aiming to achieve the inhibition of such protective immune reactions by aggressive treatment. Much should be leaned about the pathogenesis of AD.

REFERENCES


