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Autoreactive CD4⁺ T cells in Atopic Dermatitis

Eddie A. James, PhD^a and William W. Kwok, PhD^{a,b}

^aBenaroya Research Institute at Virginia Mason

^bDepartment of Immunology, University of Washington

Both environmental and genetic factors are known to contribute to the onset of atopic dermatitis (AD). Multiple genes are positively associated with AD, primarily implicating innate and adaptive immunity and epidermal barrier functions as key components of susceptibility ⁽¹⁾. Against this backdrop of genetic risk, multiple environmental factors, including exposure to allergens and infectious organisms have been implicated as disease triggers ^(2;3). In extrinsic AD, individuals develop IgE responses to food allergens, aeroallergens, and microorganisms which correlate with disease severity. Among several microorganisms associated with AD, colonization with *Malassezia sympodialis* (*M. sympodialis*) is commonly observed. However, recent reports suggest that AD may have an auto-reactive component. A recent study documented the presence of numerous specific IgEs, which cross-recognize self antigens in AD ⁽⁴⁾. In addition, AD patients with *M. sympodialis* colonization were shown to have IgE against *M. sympodialis* thioredoxin (*Mala s 13*) that cross-recognize human thioredoxin ⁽⁵⁾. These reports suggest that self-reactive IgE appears to play an important role in exacerbation of AD. Emerging evidence suggests that T cells that cross-recognize self proteins may also play an important role in AD. A 2005 study published in this journal demonstrated both IgE and T cell recognition of human manganese superoxide dismutase (MnSOD) in AD subjects that were sensitized by *Malassezia* ⁽⁶⁾. However, while this work correlated sensitization to human MnSOD with *M. sympodialis* MnSOD, it was not possible to directly demonstrate T cell cross-recognition because of the methodology employed.

In this issue of JACI, Balaji et al. demonstrated that *Mala s 13*-specific CD4⁺ T cells from AD *Malassezia* sensitized subjects were cross-reactive with human thioredoxin at a clonal level ⁽⁷⁾. These T cell clones were CLA positive (implying skin homing), secreted inflammatory cytokines, and could be isolated from both peripheral blood and skin, reinforcing their disease relevance. Most likely, these cross-reactive T cells arise through molecular mimicry. Mimicry has been implicated in other areas of allergic disease, including oral allergy syndrome in which sensitization by aeroallergens elicits food-reactive IgE and T cells ⁽⁸⁾. The study by Balaji et al. represents the best evidence that molecular mimicry between non-self (*Malassezia* proteins) and homologous self-antigens (human thioredoxin) play a role in AD at the T cell level. Notably, the vast majority of individual clones responded more vigorously to non-self, implicating *Malassezia* proteins as their primary antigen. Furthermore, Balaji et al. observed that T cells that recognized human thioredoxin could only be detected in AD subjects with *Malassezia* infection, implying that *Malassezia*-specific responses are required to elicit self-reactivity.

In detailed cytokine studies using thioredoxin-specific CD4⁺ T cells derived from skin biopsies and peripheral blood, Balaji et al. demonstrated antigen-specific Th1/Th2 profiles,

in agreement with the inflammatory/atopic nature of the disease. In addition, thioredoxin-specific cells produced IL-17 and IL-22, cytokines shown to upregulate anti-microbial peptide in keratinocytes, which plays a role anti-fungal immunity. Th17 and Th22 cells have recently been detected in the skin lesions of AD subjects ⁽⁹⁾. IL-17 is a proinflammatory cytokine capable of causing tissue damage. IL-22 is involved in epidermal remodeling and can lead to hyperplasia of keratinocytes in the epidermis ⁽¹⁰⁾. The detection of thioredoxin-specific IL-17 and IL-22 production, as shown by Balaji et al. underscores the potential importance of these cells in the disease process of AD. In addition, these cytokines were elicited through stimulation using human thioredoxin, indicating that these cytokines are a component of the self-reactive response.

Thioredoxin is a ubiquitous cellular protein and thioredoxin reactive T cells are present in peripheral blood. Therefore, it is of interest that no tissue or organ other than skin is affected by thioredoxin-specific T cell responses in these subjects. Even in healthy subjects, the human peripheral T cell repertoire includes cells that recognize self-antigens. In non-inflamed environments self-reactive T cells are typically held in check by regulatory T cells and other tolerance mechanisms ⁽¹¹⁾. However, tolerance can be broken as a result of innate and adaptive immune responses against infectious organisms such as skin infection by *M. sympodialis*. Cytokines, chemokines and other inflammatory mediators released in this context also increase apoptosis and necrosis of epithelial cells, releasing additional intracellular antigens. An analogous release of self antigens from keratinocytes after administering exogenous IFN- γ was demonstrated by Balaji et al. in their current paper. These self-antigens are processed by activated DC and presented to autoreactive T cells, releasing additional mediators and leading to a self-perpetuating cycle of inflammation. In this way, the presence of the cross-reactive T cells in the lesion could lead to chronic inflammation even after clearance of the infection. Such involvement of autoreactive T cells would contribute to the Th1 type immune responses in the chronic phase of AD. Impaired infiltration of Foxp3⁺ regulatory T cells into AD skin lesions could also contribute to this autoimmune process ⁽¹²⁾.

In spite of the promise of this interesting work, unanswered questions remain. For example, because the amino acid sequence homology between Human and *Malassezia* and thioredoxin is limited (~50%), it is unclear whether cross-reactivity is due to highly homologous conserved epitopes or whether certain sequences are cross-recognized in spite of having dissimilar amino acid sequences. Therefore, it would be interesting to define precise epitopes within Human and *Malassezia* thioredoxin. It will also be of interest to examine autoreactive T cells in AD subjects without *Malassezia* infection. AD subjects without *Malassezia* infection may be sensitized to other microorganisms, food allergens, or aeroallergens, giving rise to T cells that cross-recognize self-antigens in skin lesions. Based on the diversity of IgE binding self-antigens ⁽⁴⁾, it is likely that T cells infiltrating the lesions of AD subjects recognize multiple self antigens (in addition to thioredoxin and MnSOD) perhaps because of chronic inflammation. This would agree with the concept of antigenic epitope determinant spreading, as first proposed by Eli Sercarz, which has been verified in multiple experimental models ⁽¹³⁾. Cumulatively, those studies have shown that self-reactive T cell responses which initially recognize a single individual epitope eventually spread to other epitopes within the same antigen, and subsequently to determinants within other antigens. Therefore, it would be of great interest to determine whether additional self-reactive IgE targets which have been detected in AD subjects are also targeted by T cells.

It has long been speculated that infectious agents act as triggering agents in autoimmunity through molecular mimicry. For example, multiple sclerosis has been linked to Epstein-Barr virus infection, while Type 1 Diabetes has been linked to enterovirus virus infections ^(14;15). However, it is difficult to prove whether the infection actually causes the autoimmune

disease, because the viruses which have been implicated in disease are also prevalent in the general population. Likewise, because *Malassezia* colonization is common in both AD subjects and subjects without AD, it will be difficult to definitively prove that *Malassezia* infection triggers the initial onset of AD in susceptible subjects. However, using atopic patch test, Balaji et al. demonstrated that Mala s 13 directly induced erythema, T cell infiltrates, papules and vesicles. Thus, there seems to be little doubt that *Malassezia* infection can lead to disease exacerbation, and that because of the cross-reactivity between Mala s 13 and human thioredoxin, there is an autoimmune component of AD which plays a role in the chronic inflammatory stage of the disease. Observations from the current study also raise the possibility that autoreactive T cells can be present in a chronically inflamed environment. The broader implication is that any chronic allergic disorders could have an autoimmune component. These aspects of autoimmunity in AD and other chronic allergic disorders clearly warrant further study.

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