

Multiple Pathways Driving IgE Production and Chronic Dermatitis in Mice: A Model for Atopic Dermatitis?

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In this month's *Journal of Investigative Dermatology*, Tomimori *et al* (2004) describe interesting data derived from the study of the inbred NC/Nga mouse strain. These mice develop a spontaneous and chronic dermatitis when they live in conventional (non-sterile) animal housing conditions. These same animals, in specific-pathogen-free (aseptic) conditions, do not develop such dermatitis, suggesting that microbial flora, possibly the skin microflora, may play a critical role in such a process (Matsuda *et al*, 1997). The genetic defect(s) in these mice resulting in this chronic dermatitis are not known. What is known is that these NC/Nga mice, when living in conventional (non-sterile) housing conditions, exhibit constitutive hyperphosphorylation and exaggerated responsiveness of Janus-activated kinase 3 (JAK3). This molecule is an integral part of the signal transduction apparatus of the interleukin (IL)-4 receptor. This hyperphosphorylation of JAK3 is a finding similar to that observed in B-lymphocytes from patients with atopic dermatitis (Matusmoto *et al*, 1999). It is not known whether this is a primary defect in these NC/Nga mice or a result of inflammation due to abnormal regulation of other pathways that control inflammation or immune responses. IL-4 is a T helper (Th)-2 lymphocyte-derived cytokine known to play a role in supporting allergen-specific IgE after exposure to experimental antigens (Gauchat *et al*, 1990). Thus, the chronic activation of the IL-4 receptor signaling pathway is highly relevant to the increased serum IgE in these mice, and possibly related chronic dermatitis.

Haptens such as dinitrofluorobenzene (DNFB), when applied to the skin of normal C3H/HeN or C57BL/6 mice as a single sensitizing dose, induce allergic contact dermatitis with predominant Th1-lymphocyte immune responses (interferon (IFN)- γ -producing T cells, i.e., delayed type hypersensitivity), and no detectable hapten-specific IgE in their sera. After a sensitizing dose of hapten, however, followed by repeated elicitations on the pinna of the ear over 3–4 weeks, Th2-lymphocyte cytokine profiles appear in skin challenge sites, hapten-specific IgE becomes detectable in the sera, and immediate ear swelling responses are then observed after hapten challenge (Kitagaki *et al*, 1995). It is thought that chronic inflammation from the repeated challenges along with repetitive antigen stimulation (with possible clonal exhaustion of hapten-specific Th1-lymphocytes)

lead to the emergence of Th2-lymphocytes as the dominant effector cells under these circumstances.

In NC/Nga mice, sensitization followed by repeated challenges with haptens such as DNFB, results in chronic dermatitis and IgE overproduction, but paradoxically, in the relative absence of classic Th2-lymphocyte-derived cytokines such as IL-4. In fact, these animals exhibit excessive production of IL-12, IL-18 (both Th1-lymphocyte promoting monokines), and IFN- γ (the prototypical Th1-lymphokine) compared with a common mouse strain that responds in a typical fashion to repeated elicitations with a hapten such as DNFB. It is noteworthy that other IgE-promoting cytokines (such as IL-13) and chemical mediators (prostaglandins) were not studied, and may possibly play a role in supporting this type of immune response. It is thus possible that IL-4-independent pathways could drive this IgE response in the NC/Nga mice.

This apparently paradoxical response suggests that elevation of serum IgE can occur even in the setting of a vigorous Th1-lymphocyte immune response, and that somehow these Th1-promoting cytokines (such as IL-18) provide support in promoting allergen-specific IgE responses. Alternatively, NC/Nga mice may exhibit a resistance to the suppressive effects of the Th1-lymphocyte cytokines for the development of Th2-lymphocyte-dependent phenomenon (i.e., IFN- γ does not suppress the development of Th2-lymphocytes, and their help for subsequent IgE production). Studies of the immunology of human atopic dermatitis indicate that cytokines from Th2-lymphocytes (Yamada *et al*, 1995) as well as Th1-lymphocytes (Grewe *et al*, 1995) can be detected in skin lesions and the peripheral blood at various stages of evolution of the disease process. Thus, clinical, histologic, and immunologic studies all suggest that both Th1-lymphocytes and Th2-lymphocytes contribute to the immunopathology of human atopic disease in which both delayed type hypersensitivity (type IV allergy) and IgE-mediated processes (type I allergy) are thought to be important.

Another interesting parallel between these NC/Nga mice and the atopic dermatitis is the role of microbial flora in the disease process. It is well-known that perturbations in the skin flora of patients with atopic dermatitis, particularly overgrowth of *Staphylococcus aureus* and associated IgE-mediated immune responses against bacterial superantigens, serve as exacerbating factors for atopic skin disease (Hofer *et al*, 1999; Yarwood *et al*, 2000). NC/Nga mice living in standard (non-sterile) housing conditions exhibit sponta-

Abbreviations: IL, interleukin; TLR, toll-like receptor

neous dermatitis; those that live in a pathogen-free (sterile) environment do not exhibit spontaneous dermatitis. Thus, there is a striking parallel in these mice and patients with atopic dermatitis in their genetic propensity to respond abnormally to environmental stimuli (in this case microbial flora) with exaggerated local inflammation and a resulting dermatitis.

It is possible that toll-like receptors (TLR) may be involved in the pathophysiology of the development of aberrant IgE production and the associated dermatitis. TLR are a family of cellular receptors (10 members of the mammalian TLR have been characterized) that are critical in the innate immune response because of their ability to recognize pathogen-associated molecular patterns ("PAMP") associated with bacteria, viruses, and fungi (Takeda *et al*, 2003). Recognition of PAMP by these receptors rapidly triggers a protective inflammatory response (or danger signal) to mobilize an early innate and subsequent adaptive immune response to microbial invasion. These TLR are usually associated with antigen-presenting cells and have the capacity to shape adaptive immunity (T and B cell-mediated immune responses) by the cytokine patterns that the TLR trigger, which subsequently shape Th1- versus Th2-lymphocyte development during antigen presentation.

Potential defects in the NC/Nga mice can involve deficient signaling of TLR that result in propensity to infection or inability to clear or control colonization, or signaling through TLR that lead to cytokine patterns that would be permissive for the development of Th2 immune responses. One example of TLR signaling defects and human disease susceptibility to infection is the association of lepromatous leprosy with TLR2 signaling defects in response to *Mycobacterium leprae* lipopeptides. This receptor defect occurs because of single nucleotide polymorphisms associated with the genes encoding TLR2, rendering monocytes incapable of mounting an IL-12 response upon encountering this microbe, allowing for an unbalanced Th2-lymphocyte-dominated immune response against this mycobacterium in a subset of patients afflicted with polar (lepromatous) leprosy (Kang and Chae, 2001). Another example of how microbial products can shape adaptive immunity is the observation that certain microbial products such as peptidoglycan and lipoteichoic acid (derived from skin flora such as *S. aureus*) have been demonstrated to play a role in skewing cytokine patterns in dendritic cells via TLR2, resulting in the dendritic cell production of Th2-promoting cytokines such as IL-10, rather than IL-12 (a Th1-lymphocyte promoting cytokine), and subsequent antigen-specific IgE in response to exogenous antigen (Redecke *et al*, 2004). At the present time, there is no published evidence that NC/Nga mice exhibit

abnormalities in their TLR system, but the strong influence of their microbial flora on spontaneous dermatitis suggests that the TLR system may play a role, and this innate immune component deserves to be studied in this mouse strain.

Dissecting the mechanisms of the excessive IgE and the associated dermatitis in the presence and absence of an associated microbial flora or after repeated hapten challenges in these NC/Nga mice will provide novel insights into the understanding of the multiple pathways that drive IgE synthesis. As for human atopic dermatitis, the key components will involve a multitude of abnormalities: dysfunctional collaboration between cytokines and their receptors and their associated signal transduction pathways, immune responses by polar lymphocyte Th cell subsets, control of IgE synthesis by B-lymphocytes, and microbial-host interactions, possibly mediated by TLR activation.

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