In This Issue: Progress Towards A More Complete Understanding of Two Important Immune Diseases Involving Skin

Mark C. Udey
National Cancer Institute, NIH, Bethesda, Maryland, USA

Two articles in this issue of the JID piqued my interest because the findings have implications regarding two important dermatologic diseases. One disease (systemic sclerosis) is uncommon but particularly important because it is often devastating and our treatments are largely ineffective. The second disease (latex hypersensitivity) is much more common, running the gamut from a minor inconvenience to a life-threatening condition.

Sato and coworkers (p. 542) report in this issue of the JID that antibodies reactive with a matrix metalloproteinase are commonly found in patients with systemic sclerosis (SSc), and suggest that these antibodies may play a role in disease pathogenesis. Classified as an autoimmune disease because of the high frequency with which autoantibodies are detected and the not infrequent occurrence of sclerosis in patients with mixed connective tissue disease, the pathogenesis of SSc has been attributed to intrinsic abnormalities of fibroblasts, alterations of cytokine/growth factor production that impact in fibroblasts and/or vascular abnormalities. Ultimately, the final common pathway is inappropriate accumulation of extracellular matrix (ECM) components (especially collagen); a result that could reflect increased production of ECM, decreased degradation or both. Matrix metalloproteinases (MMPs) play a critical role in ECM degradation, and MMP-1 is essential for the initiation of degradation of the fibrillar collagens (collagens type I, II and III).

Serum was obtained from 57 Japanese patients with SSc, and autoantibodies were assessed by ELISA, Western blotting, immunofluorescence or immunoprecipitation. Controls included patients with active systemic lupus erythematosus (SLE), dermatomyositis (DM) and normal individuals. Anti-MMP-1 IgG autoantibodies were detected in 75% of patients with diffuse SSc, 15% of patients with limited SSc, 5% of patients with SLE or DM and 3% of normals. Interestingly, there was a direct correlation between SSc severity (indicated by the extent of skin sclerosis, presence of vascular abnormalities as quantified using a pulsivity index and/or pulmonary abnormalities such as reduced diffusing capacity for carbon monoxide) and the levels of anti-MMP-1 antibodies in serum. The particular relevance of anti-MMP-1 antibodies to disease pathogenesis is suggested by the observation that SSc sera with IgG anti-MMP-1 antibodies (by ELISA and Western blotting) inhibited the activity of MMP-1 *in vitro*, whereas normal sera and SSc sera that contained autoantibodies other than anti-MMP-1 did not.

Extension of these findings to other SSc patient populations will be important. It will be interesting to determine if sera from SSc patients also contain autoantibodies reactive with other MMPs or TIMPs (tissue inhibitiors of metalloproteinases). If confirmed, the results reported in this paper suggest a pathogenic role of IgG anti-MMP autoantibodies in SSc, providing a surrogate marker for disease activity that may be easier to quantify and follow serially than cutaneous sclerosis, and suggesting autoantibody production as a relevant therapeutic target. In light of this, improved, rational therapies for SSc may be on the horizon.

Good animal models of human diseases are invaluable. Indeed, lack of a mouse model that recapitulates essential features of SSc has limited progress in this disease to a significant degree. In this issue of the JID, Lehto and colleagues (p. 633) describe a new mouse model of contact sensitivity to natural rubber latex (NRL)-derived proteins, filling an important gap.

Latex hypersensitivity that results in hand dermatitis is a relatively common disorder and a significant occupational health problem. Although most individuals who are afflicted with this disease can control their symptoms by avoiding exposures to latex (usually in gloves), rare individuals are exquisitely sensitive, necessitating more stringent measures. Although contact sensitivity to highly reactive chemicals (e.g., trinitrochlorobenzene) has been extensively studied in mice, studies of contact hypersensitivity reactions to proteins in mice have been less frequent.

This model incorporates several features that are likely to be important in the pathogenesis of latex hypersensitivity in humans. Induction of a dermatitis manifested by epidermal and dermal thickening and characterized by the dermal accumulation of eosinophils and degranulated mast cells required prior disruption of the cutaneous barrier by tape stripping (injury) and chronic application of an aqueous extract of NRL proteins under hydrating conditions. Assessment of cytokine production in NRL protein-sensitized skin revealed accumulation of Th2 cytokine (IL-4) mRNA. In addition, epicutaneous application of NRL protein in the absence of adjuvant led to increased levels of total serum IgE and NRL-reactive IgE as well. Intraperitoneal administration of NRL protein in alum did not cause an increase in serum IgE and led to production of NRL-reactive IgG2a rather than IgE antibodies. Interestingly, the antibodies induced by epicutaneous and intraperitoneal sensitization also differed with regard to reactivity with two major NRL antigens. These results indicate that epicutaneous immunization with protein antigens induces an immune response with a striking Th2 bias and that route of administration can also influence immunogenicity.

The availability of this model system should facilitate additional studies of latex contact hypersensitivity. Conceivably, latex-containing products could be evaluated with regard to immunogenicity. The contribution of injury and hydration to sensitization can also be systematically explored. Finally, the efficacy of novel topical and systemic therapies that might be predicted to have efficacy in humans can be carefully tested.

Although I have focused on two papers that deal with immune-mediated diseases, the content of this issue is wide-ranging, reflecting the diversity of interests represented in the JID readership. Interested readers will find articles that additionally explore the "re-discovered" hair follicle. Studies of lipid metabolism and barrier function are included. New insights into mechanisms of apoptosis that are operative in epithelial cells are described, and medical genetics continues to be prominently represented. Finally, a treatment that may promote tolerance induction in the setting of gene therapy is described (see the Commentary by Jonathan Vogel).

0022-202X/03/$15.00