

cell suspensions in biological matrices have been used to immobilize the cells and to permit interactions with the host tissue (Lanza *et al.*, 2007). There is very little evidence that these devices—at least in the wound environment—lead to integration or long-term survival, yet there is not compelling evidence for rejection. The presumed mode of action for an LSE is paracrine stimulation, perhaps in response to the wound environment. It has been obvious for some time that these cell-based cutaneous treatments are prime candidates for genetic manipulation if safety and efficacy issues can be satisfactorily resolved. However, it is not certain that the added costs of production and safety measures can yield a cost-effective drug delivery system. Cell systems that are engineered to deliberately express one or more biologicals would fall under more stringent regulatory scrutiny. One can envisage a strategy in which cell-based healing devices are customized to deliver various doses of various factors, including proteinase inhibitors, depending on the type of wound and the stage of healing. The effects seen in this model system, which uses a human skin equivalent as opposed to intact human tissue, point in a positive direction.

CONFLICT OF INTEREST

The author states no conflict of interest.

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Filaggrin Mutations and Allergic Contact Sensitization

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In this issue, Novak *et al.* (2008) provide evidence that *filaggrin* barrier defects might also predispose to allergic contact dermatitis by allowing greater penetration of chemical haptens. Their report provides a fresh perspective on the issues of contact allergy, nickel sensitization, and stratum corneum defects.

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The eczemas comprise a family of inflammatory skin diseases that have as hallmarks itch, epidermal spongiosis, and disruption of the stratum corneum barrier. Atopic dermatitis (AD) and allergic contact dermatitis (ACD) are among the most common and widely studied of the eczemas. In the spring of 2006 a revealing new light focused on AD, firmly associating that disease with ichthyosis vulgaris and loss-of-function mutations in the *filaggrin* (*FLG*) gene (Palmer *et al.*, 2006), and subsequent studies have confirmed that finding (Irvine, 2007). This insight gave molecular support to long-standing predictions that AD might be caused by an epider-

mal barrier defect allowing penetration of irritants, microbes, and protein antigens (Wood *et al.*, 1992).

Those revelations led naturally to the question of whether *FLG* barrier defects might also predispose to ACD by allowing greater penetration of chemical haptens. In this issue, Novak and collaborators in Germany provide evidence that the answer may be yes (Novak *et al.*, 2008). These investigators looked for two common *FLG* mutations in a cross-sectional population that had been studied and patch tested with common chemicals in the KORA Allergy Study from 1994 to 1995 (Schäfer *et al.*, 2001). They selected

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1,537 subjects equally weighted for the presence of specific IgE and for a history of atopic diseases. Subjects were stratified by age and sex, and the investigators properly distinguished between patch tests showing only contact sensitization and history of actual, relevant allergy with dermatitis caused by nickel or fragrances. Results indicated associations of *FLG* mutations with nickel sensitization and with reactions to jewelry. Somewhat puzzling was the lack of an association with sensitization to other common haptens. Certainly the frequency of sensitization to preservatives and fragrance chemicals in skin-care products might be expected to be higher in the presence of a diminished barrier. It may be that the sample size in the present study was simply inadequate to provide statistically significant associations with other chemicals. Also, sensitization to such products often occurs through skin areas such as the axilla (e.g., from deodorants) or the face, which can have increased absorption, even with an intact barrier. Oddly, nickel allergy is often associated with skin piercing, which rends even the normal epidermis. Perhaps the simplistic assumption of increased nickel sensitization due to barrier impairment should be questioned and examined further in the future.

It is worth considering that the exclusive *FLG* association with nickel allergy in this study might reflect mechanisms that are more complex than the simple lack of an adequate physical barrier. Nickel and other metal ions differ from classical haptens in their capacity to activate T cells through a wide range of molecular mechanisms, some of which are dependent on antigen processing and others that are independent (Gamerding *et al.*, 2003; Thierse *et al.*, 2005). Nickel may bind to various proteins ranging from serum albumin to enzymes, chaperones, and heat shock proteins (Spiewak *et al.*, 2007). Such complexes not only may ensure transport through epidermal interstices but also may have functional effects on keratinocytes and dendritic cells (Thierse *et al.*, 2005). Protein binding by nickel might be enhanced by a preferential peptide availability caused by *FLG* mutations. Interestingly, nickel

can also bind and activate calcineurin to upregulate nuclear factor of activated T cells (NFAT) in keratinocytes (Al-Daraji *et al.*, 2002), possibly initiating inflammation that enhances allergic sensitization. For many years we have followed the well-defined concept that antigenic messages are transmitted by Langerhans cells, but we have tended to ignore possible contributions from other epidermal cells to contact sensitization until relatively recently. Studies have increasingly focused on the role of the keratinocytes in priming for eczematous inflammation (Li *et al.*, 2006).

***FLG* mutations are associated with higher frequencies of sensitization to nickel but not to other haptens.**

Nickel may have unique antigenic properties through differing associations with a variety of cells during induction of sensitization. Nickel ions, too small for antigenic recognition, are highly reactive in combining with extracellular proteins and altering spatial conformation to become allergenic. The nickel-induced changes in tertiary structure allow for dendritic cell (DC) presentation of haptenic complexes in the context of major histocompatibility complex (MHC) class II molecules to T-cell receptors (TCRs) on CD4⁺ lymphocytes (Spiewak *et al.*, 2007). Alternatively, nickel's reactivity with intracellular proteins can provide for processing and presentation, in association with MHC class I molecules, to CD8⁺ T lymphocytes. A third, metabolism-independent pathway allows direct linkage of nickel to dendritic cell MHC and to TCRs, analogous to superantigen T-cell activation (Gamerding *et al.*, 2003). Nickel may also have direct effects on DCs to enhance maturation, trigger signaling pathways, and increase expression of chemokines and costimulatory molecules (Aiba *et al.*, 2003). Hypersensitivity reactions to nickel have been reported to be represented by both T-helper 1 (Th1) and Th2 cells, although results have varied,

and this dual profile has been reported for reactions to other antigens as well (Spiewak *et al.*, 2007; Ohmen *et al.*, 1995). Overall, nickel has unique features as a contact allergen, and these may lead to a better understanding of the association with *FLG* mutations.

Another aspect relates to the complex interaction spectrum of atopy, AD, nickel sensitivity, and allergic contact reactivity. Novak *et al.* (2008) confirmed previous reports demonstrating associations between *FLG* mutations and AD and respiratory allergy (Irvine, 2007). Past studies of contact sensitivity have struggled with the paradoxical situation of impaired experimental sensitization in AD, the frequently noted association with nickel allergy (Rajka, 1989), and the higher frequency of positive patch tests in atopy and AD (Klas *et al.*, 1996). Contradictory conclusions are often noted (Spiewak, 2005), and many studies have been compromised by inconsistent definitions of atopy and AD and by concerns about irritant reactions mistaken for contact allergy (Heine *et al.*, 2004). Patients with respiratory allergies or AD have lower thresholds for irritants, possibly reflecting both barrier impairment and greater inflammatory reactivity (Nassif *et al.*, 1994). Novak and colleagues do not present data for nickel allergy in their atopic vs. nonatopic subjects but note that the association of *FLG* mutations with nickel was not related to greater sensitization in atopic individuals, referencing recent European studies (Spiewak, 2005; Heine *et al.*, 2004). The initial report of contact allergy data in this subject population showed a non-significant tendency toward a higher frequency of sensitization in the small subpopulation with AD (Schäfer *et al.*, 2001). It is possible that an increased risk of sensitization occurs only in AD individuals with *FLG* mutations or coexisting ichthyosis.

The report by Novak *et al.* provides a fresh perspective on the issues of contact allergy, nickel sensitization, and stratum corneum defects. Individuals with *FLG* mutations appear to have an increased risk of nickel sensitization. The questions of nickel sensitivity in atopics probably cannot be clarified definitively without large prospective

studies of well-characterized subjects with AD, with and without ichthyosis. Most likely, similar associations will eventually be seen for some other contact allergens. Other metal sensitivities will be an interesting area to examine. The clinical implications for ichthyosis and other barrier defects will also warrant our attention as this story unfolds.

CONFLICT OF INTEREST

The author states no conflict of interest.

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