Journal of Immunotoxicology, 2011; 8(1): 1–2

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LETTER TO THE EDITORS

Characterization of skin sensitizing chemicals: A lesson learnt from nickel allergy

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Nickel (Ni^{2+}) is the most common cause of allergic contact dermatitis. At first glance it would appear self evident that any worthwhile predictive test for the ability of chemicals to cause skin sensitization should, without difficulty, register nickel salts as clear positives. This has not been the experience however. Although nickel is in fact a comparatively weak allergen (the high prevalence of skin sensitization resulting from ubiquitous exposure, rather than potent allergenicity), the failure to engineer positive responses to this material in tests for sensitizing activity has rankled investigators. Certainly, it was our experience with the mouse local lymph node assay (LLNA) that nickel salts (and usually nickel sulfate) either failed to elicit a positive response or, less commonly, registered only very modest activity (Basketter et al., 1994). Even the adoption of different vehicles and exposure regimen failed to have a material impact on the behavior of nickel sulfate in the assay (Kimber et al., 1990; Ikarashi et al., 1992; Ryan et al., 2002). On the back of that experience, and the investigations of others, nickel has been regarded (correctly) as a "false negative" in the LLNA, and in other animal tests for measurement of skin sensitization potential.

The mouse is not completely unresponsive to nickel though and it has proven possible to elicit responses if exposure is performed together with an adjuvant, or if there is some other source of local trauma or inflammation (Sato et al., 2007). It had been proposed also that, at least in part, the unresponsiveness of mice to nickel salts might be attributable to oral tolerance (resulting from oral ingestion of metallic nickel from cage material and drinking nipples). However, even minimization of oral tolerance (and reduced activity of regulatory T-lymphocytes) failed to transform nickel into a really effective skin sensitizer in mice (Van Hoogstraten et al., 1993; Wu et al., 2007).

The mystery is now solved, the solution being that mice are different from humans.

In a very elegant paper published recently by Schmidt et al. (2010), the immunobiological bases for the observed species differences in responses to nickel have been described very convincingly. The important observation has been that nickel ions can directly trigger activation of human Toll-like receptor 4 (TLR4). This activation requires the presence of non-conserved histidine residues at positions 456 and 458 of the receptor; these residues are found on human TLR4, but not on the same receptor in mice.

The significance of this observation is that in humans, but not in mice, Ni^{2+} can induce skin sensitization because it is able, through activation of TLR4, to provoke the inflammatory signals that are required to support and sustain the initiation of an adaptive immune response. The term "danger signal" has been coined to describe the requirement that encounter with a foreign antigen is accompanied by a certain level of local trauma or cellular damage; the purpose being to prevent unnecessary and inappropriate immune responses being launched when there is no threat as signaled by the damage associated with an important antigen incursion. Such signs of damage or trauma are described collectively as pathogen-associated molecular patterns and these are recognized by cellular vectors of the immune system via pathogen recognition receptors (PRRs) (Vance et al., 2009). Of these, the most thoroughly described are the TLRs of which there are many, including TLR4 that is expressed on the plasma membrane of a variety of cell types.

We and others have drawn attention to the fact that the effective acquisition of skin sensitization is dependent upon a number of biological "hurdles" being cleared after encounter with a chemical allergen on the skin (Dearman and Kimber, 2003; Jowsey et al., 2006). Thus, a chemical must gain access to the viable epidermis so that interaction with relevant cells

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(Received 20 September 2010; revised 07 October 2010; accepted 08 October 2010)

ISSN 1547-691X print/ISSN 1547-6901 online © 2011 Informa Healthcare USA, Inc.
DOI: 10.3109/1547691X.2010.531298

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of the immune system can be effected. In addition, it is necessary that the chemical is able to form stable associations with protein to provide an immunogenic hapten-protein conjugate. A further requirement is that cutaneous dendritic cells (DCs) are mobilized to process and deliver the antigenic stimulus to peripheral lymph nodes. Alongside all of these events, we have argued that there is a need also for a certain level of inflammation such that those cytokines and chemokines that are known to be required for the activation and mobilization of DC are induced or up–regulated. The argument has been that in the absence of some local inflammatory stimulus sensitization would not be acquired, or at very least would not be acquired effectively. The assumption is that following skin contact the vast majority of chemical allergens are able to engineer some degree of local trauma, possibly involving PRR signaling (Freudenberg et al., 2009), that is sufficient to support the initiation of a cutaneous immune response and skin sensitization. Some chemical allergens are also frankly irritating to the skin and clearly there will in those instances be no lack of inflammatory signals.

Against that background, the unfolding story of allergy to nickel provides a compelling illustration of the validity of the "two signal" hypothesis as it relates to skin sensitization (McFadden and Basketter, 2000; Kimber et al., 2002). Delivery of the allergen *per se* is insufficient to ensure that immunological priming will be initiated. A second signal is required that triggers those components of the inflammatory response that are necessary for sensitization to develop. In the absence of such signals, (in mice) nickel fails to induce sensitization, but where such signals can be delivered, (in humans) nickel is allergenic—and indeed, the most common cause of allergic contact dermatitis in Europe and the United States.

Lessons learned from nickel will pay important dividends in shaping our thinking about the properties that skin sensitizers must display, and how these can be harnessed to support the development of approaches for the effective characterization of contact allergens *in vitro* and *in silico*.

Declaration of interests

The authors report no declarations of interest.

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