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COMMENTARY

Chemical allergy in humans: Fresh perspectives

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Abstract

There is considerable interest in the immunobiological processes through which the development of allergic sensitization to chemicals is initiated and orchestrated. One of the most intriguing issues is the basis for the elicitation by chemical sensitizers of different forms of allergic reaction; that is, allergic contact dermatitis or sensitization of the respiratory tract associated with occupational asthma. Studies in rodents have revealed that differential forms of allergic sensitization to chemicals are, in large part at least, a function of the selective development of discrete functional sub-populations of $CD4^+$ and $CD8^+$ T-lymphocytes. Evidence for a similar association of chemical allergy in humans with discrete T-lymphocyte populations is, however, limited. It is of some interest, therefore, that two recent articles from different teams of investigators have shed new light on the role of polarized T-lymphocyte responses in the development of allergic contact dermatitis and occupational asthma in humans. The implications for understanding of chemical allergy in humans are explored in this Commentary.

Keywords

Chemical allergy, polarized immune responses, respiratory allergy, skin sensitization

History

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The conundrum of chemical allergy

One of most intriguing aspects of chemical allergy is the fact that it can take a variety for forms. Some chemicals (contact allergens) appear preferentially to induce skin (contact) sensitization and allergic contact dermatitis, while others (respiratory allergens) favor sensitization of the respiratory tract (Kimber et al., 2011). This heterogeneity of sensitization is not attributable to differential routes of exposure, and the conclusion one must draw – for reasons we are only just beginning to understand – is that allergenic chemicals which in many respects appear to be very similar indeed (that are of low molecular weight and naturally or inducibly electrophilic) can elicit different forms of allergic sensitization (Kimber & Dearman, 2002, 2005).

One theory is that skin-sensitizing chemicals and those that cause sensitization of the respiratory tract elicit different qualities of immune response that are characterized by preferential $CD4^+$ and $CD8^+$ T-lymphocyte sub-set responses. Support for this theory derives largely from experimental studies (primarily in mice) that have revealed that in general repeated exposure to contact allergens selectively elicits T helper (T_H)-1/T-cytotoxic (T_C)-1-type immune responses, whereas respiratory allergens are associated with preferential T_H2-type responses (Dearman et al., 2005; Kimber & Dearman, 1998). Based on these observations, the speculation has been that contact and respiratory chemical allergens are recognized and handled differently by the immune system. Clearly the adaptive immune system has not evolved for the specific purpose of providing a mechanism for responding to chemical allergens, the implication being that allergic sensitization to otherwise innocuous chemicals and proteins is a result of their misrecognition by the immune system as potentially pathogenic micro-organisms. There flows from this the suggestion that, in sensitized subjects, specific contact allergens have been misread as pathogenic viruses or bacteria against which the immune system deploys T_H1-type responses. The corollary is that chemical respiratory allergens are being recognized inappropriately as parasite antigens that drive T_H2-type immune responses.

While the above is an attractive and plausible hypothesis and is consistent with the polarization of immune responses to contact and respiratory chemical allergens that is observed in mice, evidence for similar polarization of human immune responses to contact allergens is not so readily available.

Immune responses to chemical allergens in humans

It is true that, in humans, certain chemicals or classes of chemicals favor the induction of respiratory allergy and occupational asthma. Included among these are the diisocyanates, acid anhydrides, chloroplatinate salts, and certain reactive dyes (Kimber et al., 2011). However, although each of these chemical groupings is associated primarily with occupational asthma, there are for at least some of these chemicals sporadic reports of allergic contact dermatitis. It also appears that other allergenic chemicals (much larger in number) preferentially cause skin sensitization and allergic contact dermatitis. For many contact allergens, despite evidence of widespread human exposure (2,4-dinitrochlorobenzene [DNCB], eugenol, and isoeugenol, for instance), there is no evidence to suggest they have the ability to cause sensitization of the respiratory tract. However, caution is necessary, and it has to be acknowledged that the absence of evidence for the ability of contact allergens to induce respiratory

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sensitization (as well as skin sensitization) does necessarily not provide persuasive evidence for the absence of the potential to do so. Nevertheless, it does appear that in humans, as in mice, chemical allergens display some selectivity with respect to the form that sensitization will take.

What is less certain is the extent to which immune responses to chemical allergens in humans display polarizations similar to those seen in mice. There is no reason why the form allergic reactions to chemicals preferentially take in humans should not be underpinned by qualitative differences in immune responses, but there is simply little evidence available to confirm this. In this context, there have been two recent papers (from different teams of investigators) that provide intriguing insights into human immune responses to chemical allergens.

The first of these described studies examining skin sensitization of subjects to DNCB (Newell et al., 2013). These investigators sought to compare the effectiveness of sensitization to DNCB in normal controls with patients diagnosed with mild-to-severe atopic dermatitis. An important question addressed was whether patients with atopic dermatitis were able to acquire and sustain normal levels of sensitization to a contact allergen. The question is important because skin sensitization is almost always associated with selective T_H1/T_C1-type responses, whereas atopic dermatitis (in common with other forms of atopic disease) is characterized by a selective T_H2 immune phenol-type. It was found that sensitization to DNCB through uninvolved skin in patients with atopic dermatitis was less effective than was sensitization of control subjects; challenge-induced allergic reactions were significantly less vigorous in subjects with atopic dermatitis (Newell et al., 2013). The less effective acquisition of skin sensitization was associated in atopic dermatitis patients with a skewing of the immune response provoked by exposure to DNCB towards a T_H2 phenotype. In the control group, persistent T_H1 type responses were observed (Newell et al., 2013).

A number of interesting inferences can be drawn from these data. The first is that, under normal circumstances, successful/optimal skin sensitization to DNCB is characterized by elicitation of preferential T_H1-type responses. However, under circumstances where the T_H2-type responses will be favored (in the case of the study summarized above, where there is an atopic phenotype), then the quality of immune response provoked by exposure to DNCB (and presumably other contact allergens) will be skewed away from T_H1 selectivity and a preferential T_H2 response will be favored. As observed by Newell et al. (2013), in those instances where polarization towards T_H1-type responses is compromised, then skin sensitization will be less effective (measured as a function of less vigorous challenge-induced elicitation reactions).

Collectively, these data argue that polarization of immune responses elicited in response to a chemical allergen is able to influence the acquisition of sensitization. In the investigations reported by Newell et al. (2013), it was clear that the balance between T_H1 and T_H2 polarization influences significantly the development of skin sensitization. What is not known, however, but would be of considerable interest, is whether conventional exposure of patients with atopic dermatitis to DNCB also has the potential to cause sensitization of the respiratory tract.

The second article (Ouyang et al., 2013) focused instead on occupational asthma caused by exposure to diisocyanates. As indicated above, diisocyanates are a class of chemicals that are known to cause allergic sensitization of the respiratory tract and occupational asthma. There is a general assumption, based on relatively little evidence, that sensitization is effected through T_H2 immune responses. The situation is complicated, however, because with some chemical respiratory allergens, including diisocyanates, it has not been possible to show a clear association between clinical symptoms and the presence of serum IgE antibodies.

In a search for novel biomarkers of occupational asthma, Ouyang et al. (2013) examined the methylation status of the promoter region of a small number of candidate genes. The investigators recorded a significant increase in the methylation of the promoter for interferon (IFN)-γ in patients with confirmed occupational asthma to diisocyanates compared with relevant control groups. This is a tantalizing observation because IFNγ is an important Type 1 cytokine, produced by T_H1 and T_C1 cells that promotes Type 1 responses and down-regulates T_H2 responses. The evidence suggests that there is epigenetic regulation of IFNγ in patients with occupational asthma to diisocyanates. Hyper-methylation of the promoter region of the *ifn*-γ gene will result in a reduced production of this cytokine that will in turn favor the selective differentiation of T_H2 cells and the development of preferential T_H2-type responses. The interpretation is that, in common with observations made in mouse studies, occupational asthma in humans may be associated with, and facilitated by, events and immunological processes that favor skewing of immune responses to a preferential T_H2 phenotype.

Concluding comments

This short commentary does not, and cannot, provide exhaustive evidence that immune responses elicited in humans by different forms of chemical allergens are associated with, and driven by, the development of polarized T-lymphocyte sub-sets. Clearly, to confirm that such polarized responses in humans determine the phenotype of allergic reactions will require investigations using well-defined cohorts of patients with confirmed allergic contact dermatitis or chemical respiratory allergy. In advance of that, the two recent papers cited here provide intriguing insights into the possible critical role of functional sub-populations in shaping allergic responses to chemicals. If such can be confirmed and characterized more fully, then not only does this provide important opportunities to inform management of chemical allergy in humans, it will also underpin approaches to develop improved approaches for hazard characterization, and for the identification of inter-individual susceptibility factors. These recent articles have whetted appetites for confirmatory research.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this Commentary.

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