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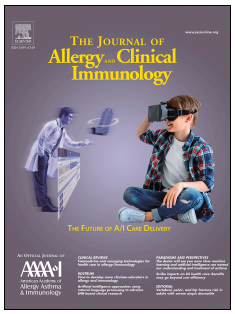

Contact allergy across the human lifespan

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Prevalence of hapten-specific contact allergy varies with age

Contact allergy is a common T-cell mediated inflammatory dermatosis with an estimated point prevalence of 20.1% in the general population (1). Its development consists of two steps, sensitization and elicitation, which are triggered by skin contact with environmental chemicals (haptens). Thus, its epidemiology, as measured by patch testing that recapitulates elicitation reactions, varies temporally and spatially according to factors that determine hapten exposure. A classic example of this has been the introduction of the European Union Nickel Directive in 1994 that resulted in a declining prevalence of nickel-specific contact allergy in Denmark, Germany, Italy and the United Kingdom (2).

Age is also recognised as an important determinant of contact allergy. Meta-analysis of population-based studies has shown that it is generally more prevalent in adults (21.4%) compared with children (16.5%) and analysis of individual haptens has demonstrated specific profiles of age-related variation (1, 3). For example, nickel demonstrates a peak prevalence amongst patch-tested populations in early adulthood that slowly declines with age (**Figure 1a**). In contrast, prevalence of contact allergy to fragrance substances increases until extreme old age (**Figure 1b**), while the rising prevalence of contact allergy to preservatives, e.g., methylisothiazolinone (MI) and methyldibromo glutaronitrile (MDBGN), plateaus at approximately 70 years (**Figure 1c**). Although these profiles of age-related variation may be partially attributable to differential hapten exposure patterns across the lifespan, there is evidence suggesting contributions by physiological aging of innate and adaptive immune responses to these phenomena.

The aging skin barrier and innate immunity in contact allergy

The skin barrier and innate immunity play important roles in sensitization and elicitation reactions by permitting percutaneous penetration of haptens and providing “danger signals” that activate pro-inflammatory adaptive immune responses. Skin penetration by haptens may rise with age due to barrier impairment, which is characterised by reduced lipid content and increased susceptibility to damage as a result of poor keratinocyte adhesion (4). However, the concomitant ability of haptens to trigger appropriate innate immune response may also decline. Langerhans

cells are less frequent and migrate poorly in the elderly, while aged dermal dendritic cells have demonstrated poor migration, phagocytosis of antigen and ability to activate T-cells (4). Considering these observations together, it is unclear what influence aging of the skin barrier and innate immunity might have on profiles of contact allergy across the lifespan.

The aging adaptive immune system in contact allergy

T-cells are the primary effector cells in allergic contact dermatitis and changes in their functional activity are most likely responsible for alterations in susceptibility observed in the elderly. We shall therefore dedicate the remainder of this review to discussion of evidence supporting a contribution by age-related changes in T-cell function to hapten-specific allergic profiles across the lifespan.

Susceptibility to experimental sensitization by haptens reduces with age

Mice and humans clearly demonstrate an age-related reduction in susceptibility to contact sensitization, and this is consistent with the view that the vigor and effectiveness of the adaptive immune system declines with increasing age. Roupe *et al.* demonstrated an age-dependent decline in effective sensitization to picryl chloride in mice (5). Similarly, Girard *et al.* sensitized patients topically to dinitrochlorobenzene and observed that 44 of 46 (96%) of those aged 20–40 years developed contact allergy when re-challenged three weeks later, whereas only 10 of 44 (23%) patients aged greater than 65 years became sensitized (6). Although investigations of skin-specific T-cell responses in old age are limited, these observations correlate strongly with investigations demonstrating that blood-derived T-cells have diminished responses following direct activation and treatment with mitogenic stimuli. Unfortunately, these studies did not distinguish between naïve and memory T-cell subsets within the responding populations, and thus, it remains unclear whether naïve T-cells are functionally impaired or simply less abundant compared to memory subsets (7).

Hapten-specific profiles of contact allergy across the lifespan – paradoxical observations

It is possible to account for an age-related decline in nickel allergy via differential exposure patterns and waning effector T-cell responses with age (**Figure 1a**). Contact sensitization facilitated by activation of naïve T-cells is clearly reduced, while clinical observations of delayed

or less vigorous patch test reactions amongst the elderly with nickel allergy imply that elicitation reactions mediated by nickel-specific memory T-cells are also affected. Nevertheless, this model does not account for an age-related increase in prevalence of contact allergy to other haptens such as fragrance substances, MI, and MDBGN (**Figure 1b-c**). Furthermore, epidemics of contact allergy question explanations whereby differential or cumulative hapten exposure across the lifespan solely account for this paradox.

An epidemic of MI contact allergy developed around 2010 following a change to European legislation in 2005 that allowed its use as a single-agent preservative in cosmetics up to a concentration of 100 ppm, and in industrial products with no limitations. It had previously only been used in concentrations up to 5 ppm in cosmetic products and 15-55 ppm in industrial products. Interestingly, this epidemic disproportionately affected those aged over 40 although MI was ubiquitous in personal and household products used by all age groups (8). This argues against differential exposure between young and old as the explanation for a predilection to MI contact allergy in older people. Furthermore, a similar epidemic disproportionately affecting older individuals developed following the introduction of MDBGN as a *de novo* ubiquitous preservative in personal care products in 1985, confirming that cumulative exposure cannot always account for increasing contact allergy with age (9).

Increased prevalence of hapten-specific contact allergy infers a role for senescent immunoregulatory responses

Regulatory T-cells (T_{reg}) play an important role in the modulation of both sensitization and elicitation reactions in contact allergy. T_{reg} cells have been shown to prevent sensitisation and maintain tolerance to certain haptens under conditions of low-dose continuous skin exposure, also known as “low zone tolerance”. Similarly, experiments have demonstrated that elicitation of nickel allergy, which is mediated by $CD8^+$ effector T-cells, can be attenuated by $CD4^+$ T_{reg} cells. Thus, the manifestation of contact allergy is likely to be influenced by a delicate balance between effector and regulatory arms of the T-cell compartment (10).

Age-related aberrations in this delicate balance may thus account for increasing contact allergy to fragrance substances, MI and MDBGN in the elderly, despite declining susceptibility to

contact sensitization and a lack of differential exposure between aged and young individuals. These haptens are ubiquitous in both personal and household products and yet contact allergy to them at a population-level is rare. This suggests that a population majority are exposed from youth onwards and yet remain tolerized, possibly via the phenomenon of "low-zone tolerance". Increasing contact allergy with age therefore infers a role for age-related attrition of T_{reg} responses that would normally maintain tolerance and prevent elicitation reactions. This model would certainly account for the inexorable increase fragrance substance allergy with age, however, the plateau in prevalence of MI and MDBGN allergy at approximately 70 years suggests that age-related attrition of effector and regulatory T-cell responses may combine differently throughout the aging process.

This model is supported by previous studies demonstrating an accumulation of T_{reg} cells in the blood of aged Balb/c mice with reduced ability to suppress interleukin-2 release by effector T-cells (3). A similar age-related increase in T_{reg} cells is observed in human skin, although the quality of their responses is uncertain. Nonetheless, observations of increasing skin infections and cancer alongside increasing skin-specific autoimmunity with age supports the notion that age may have divergent effects on T_{reg} responses (4).

Conclusion

Patterns of contact allergy across the lifespan illustrate a complex interaction of environmental haptens with the aging skin barrier and immune system. Declining effector T-cell responses to certain haptens, e.g., nickel, likely contribute to reduced sensitization and elicitation reactions in the aged. In contrast, the role of regulatory T-cells is more complex but clinical observations infer a contribution by diminishing regulatory responses to the increasing prevalence of certain contact allergies with age. Investigation of skin-specific T-cell responses in the aged is required to provide further insights into these phenomena.

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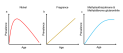
170 **Figure 1. Hapten-specific profiles of contact allergy across the lifespan (a)** Nickel **(b)**
171 Fragrance substances **(c)** Methylisothiazolinone and methyldibromo glutaronitrile



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