

Immunology of Allergic Contact Dermatitis

Allergic contact dermatitis is a T cell immune mediated inflammatory skin condition. It is characterized by the following immunological properties:

- **Immunological memory:** induction of sensitization. When a contact allergen penetrates and reacts covalently with protein in the skin, it is transported to the local lymph node by antigen presenting cells. There, it is presented to naive T cells through interactions between the haptenized antigen-peptide complex, Major Histocompatibility Complex (MHC) groove, and T cell receptor. On recognition of the antigen and in the presence of danger signals, a naive T cell will undergo clonal proliferation to produce memory and effector T cells.
- **Elicitation:** repeated exposure to the antigen will cause further clonal proliferation until a threshold is surpassed when the pool of cloned T cells recognizing the antigen is sufficiently large that when the antigen is encountered within the skin, the T cells will activate and initiate local dermal inflammation.
- The *Th1* and *Th17* immune pathways are predominantly involved with the production of pro-inflammatory cytokines such as IL-1, IL-2, tumor necrosis factor- α (TNF- α), α -interferon, IL-6, IL-8, IL-12, IL-17, and IL-23 [1].
- **Friedmann's principle:** the single most important factor in sensitization is allergen dose per unit area of skin (except for areas of skin less than 1 cm² when the aggregate dose is paramount). Therefore, someone who sprays perfume for 2 seconds on just a small area of the neck is more likely to become sensitized to the fragrance allergen(s) than someone who sprays the perfume for 2 seconds all over the torso [2].
- Contact allergens are *haptens*, which are protein reactive and bind chemically to proteins/peptides within the skin. Contact allergens/haptens are usually electrophilic and form covalent bonds with nucleophilic amino acids such as lysine, cysteine, and/or histidine [3]. Sometimes the contact allergen needs to be first oxidized (pre-hapten) or metabolized (pro-hapten) before becoming sufficiently electrophilic. The altered peptide/protein is then recognized by the immune system.
- **Danger signals** (Figure 1.1). Contact allergens/haptens also stimulate the innate immune system, which then alerts the adaptive immune system. It usually achieves innate immune activation through the generation of reactive oxygen species (ROS)/oxidative stress which then generates danger-associated molecular pattern (DAMP) molecules such as fibronectin and hyaluronan [4]. These DAMP molecules then activate pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) 2 and 4, which leads to the stimulation of pro-inflammatory cytokines, the secretion of chemokines and recruitment of T cells to the skin, and an amplification of the immune response [1].
- Metal contact allergens appear to be unique in having the ability to directly stimulate TLRs, and hence the innate immune system, without generating DAMP molecules [5].
- **Immunological mechanisms** underpinning allergic contact dermatitis have similarities to the immune response to pathogenic bacteria and this explains why apparently evolutionarily wasteful responses (allergic contact dermatitis) have been preserved [1, 6].
- There is strong clinical evidence that the immune response to contact allergy consists of both a tolerizing and a sensitizing response, and that the tolerizing response decays with age at a faster rate than the sensitizing response. This explains why allergic contact dermatitis is more common in the elderly, when the T cell sensitizing response to experimental strong contact allergens such as dinitrochlorobenzene (DNCB) appears to decline [7].
- Exposure to contact allergens in the absence of danger signals should theoretically lead to tolerance. However, once clinical sensitization has occurred it has not so far been possible to reverse it [8].
- **Oral tolerance** to nickel through dental braces has probably occurred in many individuals; however, this effect will usually only happen if the individual has not had their ears pierced prior to dental braces being inserted such that they have significant prior skin exposure [9].
- In everyday life, most allergic contact dermatitis reactions are elicitation reactions and occur within 48 hours of exposure. A main exception to this is reaction to *p*-phenylenediamine in "henna beach tattoos", which is usually a primary sensitizing reaction occurring after 10–21 days, similar to an experimental DNCB sensitizing reaction.

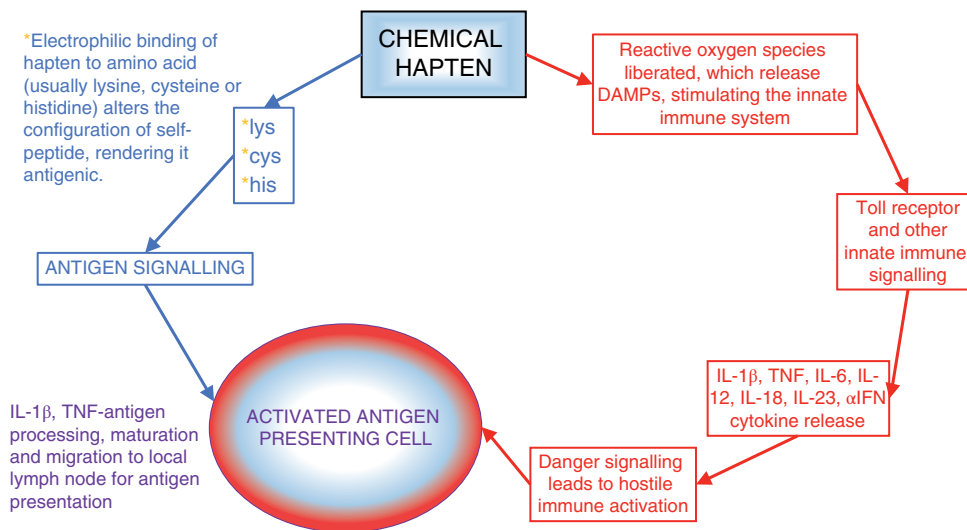


Figure 1.1 Dual signaling by haptens leading to contact sensitization. $\rightarrow$, antigen pathway; $\rightarrow$, danger pathway.

- By inference, sensitization to everyday agents such as cosmetic allergens are “quiet” events. Elicitation allergic contact dermatitis reactions occur when the threshold for response is surpassed, recognizing that the threshold will depend on the dose/concentration of the allergen factored with the extent/level of sensitization.
- The level of sensitization can increase through either repeated exposure to an allergen from a single source (e.g. *p*-phenylenediamine exposure from hair dye repeatedly applied every 1–2 months) or from exposure to an agent from multiple sources (e.g. methylisothiazolinone exposure from cosmetic creams, shampoos, and washing-up liquid).
- The immunological dose can increase through exposure to increased concentrations of an allergen (e.g. changing from blonde to black hair dye can increase the allergen exposure by a factor of 10 [10]), exposure to an allergen in the presence of an adjuvant (e.g. fragrance exposure in the presence of an aluminum salt in a deodorant, the aluminum salt acting as an adjuvant and increasing the danger signals generated), exposure to an allergen on skin which is already inflamed and where danger signals have already been generated (e.g. application of fragrance in an aftershave onto facial skin with seborrheic eczema), or increased time of exposure to an allergen (e.g. increased work hours in a construction unit leading to increased time of exposure to epoxy resin).
- Some contact allergens co-react from immunological cross-reaction due to chemical similarity, e.g. nickel and palladium, *p*-phenylenediamine and benzocaine. Some contact allergens co-react due to sensitization from same-source exposure, e.g. nickel and cobalt from exposure to low-carat gold jewelry.
- In patients with atopic dermatitis, contact sensitization occurs through the Th2 immune system and is therefore less efficient [11]. This may also explain how contact allergens and exposure to irritants can exacerbate atopic dermatitis (i.e. through Th2 stimulation) even without sensitization occurring (chemical atopy) [12].

References

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