HYPERSENSIBILITE RETARDEE
Physiopathologie

Cours du DESC/Capacité
Allergologie et Immunologie Clinique
Rhone-Alpes-Auvergne

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The variants of delayed hypersensitivity

<table>
<thead>
<tr>
<th>delayed reaction</th>
<th>maximal reaction time</th>
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<tr>
<td>contact</td>
<td>48–72 hours</td>
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<tr>
<td>tuberculin</td>
<td>48–72 hours</td>
</tr>
<tr>
<td>granulomatous</td>
<td>21–28 days</td>
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**Fig. 24.1** Contact and tuberculin-type hypersensitivity have a similar time course and are maximal at 48–72 hours. In certain circumstances (e.g. with insoluble antigen) granulomatous reactions also develop at 21–28 days (e.g. skin testing in leprosy).
Fig. 24.2 Clinical and patch-test appearances of contact hypersensitivity. (1) The eczematous area at the wrist is due to sensitivity to nickel in the watch-strap buckle. (2) The suspected allergy may be confirmed by applying potential allergens, in the relevant concentrations and vehicles, to the patient’s upper back (patch testing). A positive reaction causes a localized area of eczema at the site of the offending allergen, 2–4 days after application.
Fig. 24.4 The hapten forms a hapten-carrier complex in the epidermis. Langerhans’ cells internalize the antigen, undergo maturation, and migrate via afferent lymphatics to the paracortical area of the regional lymph node where peptide/MHC complexes on the surface of the Langerhans’ cell can also be directly haptenated. As interdigitating cells, they present antigen to CD4+ T cells.
Elicitation phase of contact hypersensitivity

Fig. 24.5 Langerhans' cells carrying the hapten-carrier complex (1) move from the epidermis to the dermis, where they present the hapten-carrier complex to memory CD4+ T cells (2). Activated CD4+ T cells release IFNγ, which induces expression of ICAM-1 (3) and, later, MHC class II molecules (4) on the surface of keratinocytes and on endothelial cells of dermal capillaries and activates keratinocytes which release proinflammatory cytokines such as IL-1, IL-6 and GM-CSF (5). Non-antigen-specific CD4+ T cells are attracted to the site by cytokines (6) and may bind to keratinocytes via ICAM-1 and class II molecules. Activated macrophages are also attracted to the skin, but this occurs later. Thereafter the reaction starts to downregulate. This downregulation may be influenced by eicosanoids such as PGE, produced by activated keratinocytes and macrophages (7).
Fig. 24.8  Clinical and histological appearances of tuberculin-type sensitivity. The response to an injection of leprosy bacillus into a sensitized individual is known as the Fernandez reaction. The reaction is characterized by an area of firm red swelling of the skin and is maximal 48–72 hours after challenge (1). Histologically (2), there is a dense dermal infiltrate of leucocytes H&E stain, ×80.
Fig. 24.9  This diagram illustrates cellular movements following intradermal injection of tuberculin. Within 1–2 hours there is expression of E-selectin on capillary endothelium leading to a brief influx of neutrophil leucocytes. By 12 hours ICAM-1 and VCAM-1 on endothelium bind the integrins LFA-1 and VLA-4 on monocytes and lymphocytes, leading to accumulation of both cell types in the dermis. This peaks at 48 hours and is followed by expression of the HLA class II molecules on keratinocytes. There is no oedema of the epidermis.
Fig. 24.12  Clinical and histological appearances of the Mitsuda reaction in leprosy seen at 28 days. (1) The resultant skin swelling (which may be ulcerated) is much harder and better defined than at 48 hours. (2) Histology shows a typical epithelioid-cell granuloma (H&E stain, ×60). Giant cells (G) are visible in the centre of the lesion, which is surrounded by a cuff of lymphocytes. This response is more akin to the pathological processes in delayed hypersensitivity diseases than the self-resolving tuberculin-type reaction. The reaction is due to the continued presence of mycobacterial antigen.
<table>
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<tr>
<th>Syndrome</th>
<th>Antigen</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Delayed-type hypersensitivity</td>
<td>Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)</td>
<td>Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis</td>
</tr>
<tr>
<td>Contact hypersensitivity</td>
<td>Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate</td>
<td>Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses</td>
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<tr>
<td>Gluten-sensitive enteropathy (celiac disease)</td>
<td>Gliadin</td>
<td>Villous atrophy in small bowel Malabsorption</td>
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</table>

Figure 12-24 Immunobiology, 6/e. (© Garland Science 2005)
Antigen is injected into subcutaneous tissue and processed by local antigen-presenting cells.

A $T_H^1$ effector cell recognizes antigen and releases cytokines which act on vascular endothelium.

Recruitment of phagocytes and plasma to site of antigen injection causes visible lesion.

24–72 hours
Antigen is processed by tissue macrophages and stimulates $T_H^1$ cells.

$T_H^1$ induces the release of:
- Chemokines
- Cytokines
- Cytotoxins

- Chemokines:
  - Recruit macrophages to site of antigen deposition

- IFN-γ:
  - Induces expression of vascular adhesion molecules
  - Activates macrophages, increasing release of inflammatory mediators

- TNF-α and TNF-β:
  - Cause local tissue destruction
  - Increase expression of adhesion molecules on local blood vessels

- IL-3/GM-CSF:
  - Stimulate monocyte production by bone marrow stem cells

Figure 12-26 Immunobiology, 6/e. (© Garland Science 2005)
Contact-sensitizing agent penetrates the skin and binds to self proteins, which are taken up by Langerhans' cells

Langerhans' cells present self peptides haptented with the contact-sensitizing agent to $\text{TH}_1$ cells which secrete IFN-γ and other cytokines

Activated keratinocytes secrete cytokines such as IL-1 and TNF-α and chemokines such as CXCL8 (IL-8), CXCL11 (IP-9), and CXCL9 (Mig)

The products of keratinocytes and $\text{TH}_1$ cells activate macrophages to secrete mediators of inflammation

Figure 12-27 Immunobiology, 6/e. (© Garland Science 2005)
Réaction retardée (réponse cellulaire)
Exemple de l’allergie au nickel (bijoux fantaisie)

**Acte I : sensibilisation**

1. L’allergène est en contact avec la peau.

2. Il est pris en charge par les cellules dendritiques.

3. Les cellules dendritiques migrent vers les ganglions lymphatiques. Là, elles présentent l’allergène aux lymphocytes T qui sont alors activés.

**Acte II : réaction retardée**

1. L’allergène rentre à nouveau en contact avec la peau.

2. Il est pris en charge par les cellules dendritiques qui font alors intervenir les lymphocytes T précédemment activés.

3. Les lymphocytes T sécrètent des molécules qui attirent différentes cellules de l’inflammation (globules blancs) dans la peau.

4. Les lymphocytes T activés migrent dans les vaisseaux sanguins, puis dans la peau.

Un ou deux jours plus tard, les globules blancs accumulés provoquent une réaction allergique : un eczéma plus ou moins localisé, appelé aussi dermatite de contact.
Type IV allergic hypersensitivity in allergic contact dermatitis

Skin tests represent experimental models of allergic type IV DTH reactions
<table>
<thead>
<tr>
<th>Extended Coombs and Cell Classification†</th>
<th>Type of Immune Response‡</th>
<th>Pathologic Characteristics</th>
<th>Clinical Symptoms§</th>
<th>Covalent and Noncovalent Drug Binding$</th>
<th>Cell Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>IgE</td>
<td>Mast-cell degranulation</td>
<td>Urticaria, anaphylaxis</td>
<td>Covalent drug binding</td>
<td>B cells/IgE</td>
</tr>
<tr>
<td>Type II</td>
<td>IgG and FcR</td>
<td>FcR–dependent cell destruction</td>
<td>Blood cell dyscrasia</td>
<td>Covalent drug binding</td>
<td>B cells/IgE</td>
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<tr>
<td>Type III</td>
<td>IgG and complement or FcR</td>
<td>Immunocomplex deposition</td>
<td>Vasculitis</td>
<td>Covalent drug binding</td>
<td>B cells/IgE</td>
</tr>
<tr>
<td>Type IVa</td>
<td>Th 1 (IFN-γ)</td>
<td>Monocyte activation</td>
<td>Eczema</td>
<td>Covalent and noncovalent drug binding</td>
<td>T cells</td>
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<tr>
<td>Type IVb</td>
<td>Th 2 (IL-5 and IL-4)</td>
<td>Eosinophilic inflammation</td>
<td>Maculopapular exanthema, bullous exanthema</td>
<td>Covalent and noncovalent drug binding</td>
<td>T cells</td>
</tr>
<tr>
<td>Type IVc</td>
<td>CTL (perforin and granzyme B)</td>
<td>CD4+ or CD8-mediated killing of cells (i.e., keratinocyte)</td>
<td>Maculopapular exanthema, eczema, bullous exanthema, pustular exanthema</td>
<td>Covalent and noncovalent drug binding</td>
<td>T cells</td>
</tr>
<tr>
<td>Type IVd</td>
<td>T cells (IL-8)</td>
<td>Neutrophil recruitment and activation</td>
<td>Pustular exanthema</td>
<td>Covalent and noncovalent drug binding</td>
<td>T cells</td>
</tr>
</tbody>
</table>

* CTL = cytotoxic T cells; FcR = Fc receptor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; Th = T helper.
† Based on reference 10.
‡ Only the dominant reaction is shown. In maculopapular exanthema, type IVb and IVc reactions can occur together; in pustular exanthema, type IVb, IVc, and IVd can occur together; and in bullous exanthema, type IVc with IVb, IVa, or both can occur together. In most instances, I type predominates clinically (type IVc in maculopapular and bullous exanthema, type IVd in pustular exanthema). See text.
§ Covalent binding can elicit both T-cell– and B-cell–mediated immune reactions, while noncovalent presentation may elicit exclusive T-cell reactions. See text.
‖ T-cell help for Ig (e.g., IL-4, IL-5, IFN-γ).