Basic Immune Functions

The immune system is designed to defend the body in a safe and efficient way against a variety of potentially dangerous materials including toxins and infectious organisms. There are many components to this defense system. Mechanical and biological barriers prevent the penetration of exogenous materials into the body (p. 1). Only after these barriers have been breached and cells have been directly attacked does the immune system come into play.

Certain immune cells can directly phagocytose and destroy many pathogens by a variety of mechanisms. To accomplish this, they require the close cooperation of the somatic cells, which both alert the immune system through alarm signals and then later participate in the effector phase. These signals can be grouped together as “stress signals.” This initial, nonspecific immune response is known as the innate immune response. Apparently, all cells can participate to an extent in this process. The major players are those cells that are first or most often attacked. Thus, in the skin it is the keratinocyte; in the mucosa it is the epithelial cell; in the liver it is the hepatocyte. Other cells, generally thought of as structural and not active, such as glial cells and fibroblasts, are also involved in innate immunity.

In response to stress signals, these cells respond with the release of a variety of messengers (p. 18f) that attract and activate phagocytic antigen-presenting cells (APC) (p. 12f) and thus initiate the specific immune response. Once activated, APC carry processed foreign antigens from the site of injury and migrate via the lymphatics to the regional lymph nodes, where they secrete chemokines to attract naive CD4 and CD8 T cells (p. 14f). The APC present the foreign antigen peptide to these T cells. Those naive cells that recognize the foreign peptide on the basis of their receptor structure are in turn stimulated and differentiate into blast cells. These activated T cells now express different surface antigens that make them capable of responding to growth factors, leaving the lymph nodes and themselves secreting cytokines. Exactly which mediators are involved and how the T cells in the end interact with their target cells and antigens is quite dependent on how they are activated (p. 14f).

The first important task for the activated T cells is clonal proliferation to ensure that enough cells are available to react in a specific fashion against the alarm-triggering noxious or infectious agent. Such specialized T cells can increase their number by a factor of 10,000 over a period of a few days under the influence of the cytokine interleukin 2 (IL-2) (p. 14f). Activated T cells have many other tasks. They interact closely in the lymph nodes with B cells, giving them signals for immunoglobulin production (p. 16f). Finally, they leave the lymph nodes and return to the initial site of injury. This return is made possible because the innate immune response has already started an inflammatory process at this site, leading to the production and expression of a variety of adhesion molecules. Certain vascular adhesion molecules specifically allow the activated T cells to attach to the vessel wall, migrate through the wall, and then reach the inflamed tissue. There the activated T cells are stimulated again—most likely by antigen-laden monocytes and macrophages—to produce a wide variety of pro-inflammatory mediators.

Interferon $\gamma$ (IFN-$\gamma$) plays a major role at this stage. It triggers the macrophages to produce inflammatory mediators, which in turn further stimulate the neighboring cells to produce free radicals, tumor necrosis factor (TNF), and other factors with which they had initially triggered the immune response. Compared to the initiation phase, at this stage both the magnitude of the response and the spectrum of cytokines secreted is much greater (p. 18f). The initial nonspecific immune response is so effectively increased by the appearance of these microbe-specific or toxin-specific T cells that the local inflammatory response becomes capable of destroying the infected cells. This inactivates the invading micro-organisms and may expel or control foreign material.
Specific and Nonspecific Defenses

A. Mechanical Barriers

Activated keratinocytes and epithelial cells (also fibroblasts and endothelial and stromal cells)

B. Nonspecific Immediate Response

Inflammatory mediators TNF, IL-1, IL-10, IL-15, ...

Expression of immune molecules, e.g., MHC II

Expression of adhesion molecules

B. Nonspecific Immediate Response

Activation of specific response

Activated T cell

TH1

TH2

Activated macrophages

IFN-γ IL-2, 4, 5

Activation of macrophages

B cell

Plasma cell

C. Specific or Adaptive Immune Response
A. Type IV Reaction

The Type IV reaction is functionally best described as cell-mediated or delayed-type hypersensitivity reaction (DTHR). In contrast to the other three types of allergic reactions, which are antibody-mediated, DTHR is driven by immune cells that interact directly with antigen-laden cells. In sensitized individuals a DTHR requires 1–3 days to reach maximum strength and is directed by T cells. One also speaks of “delayed” or “T cell-mediated” reactions. The T cells are responsible for two distinct forms of DTHR mediated by:
- CD4 T cells (helper T cells or TH cells)
- CD8 T cells (cytotoxic T cells or CTL)

Clinical forms of Type IV allergy. The Type IV reaction is always directed against antigens that are presented as a peptide or hapten bound to the MHC class I or class II molecules on a cell. Classical examples of DTHR are the protective reactions against mycobacterial or Trichophyton infections. Not all Type IV reactions are protective; in allergic contact dermatitis, the body reacts against otherwise harmless antigens such as preservatives in medications or nickel in jewelry. Finally, organ-specific autoimmune reactions can arise when the target antigens are the body’s own cellular glycoproteins.

B. CD4+-mediated Immune Reaction

The crucial cells for a DTHR are CD4 memory T cells of the Th1 type producing IFN-γ. Following the initial activation via DC and antigen and the subsequent resolution of the acute inflammatory reaction, a population of already-activated memory T cells remains. They are characterized by the expression of CD45RO instead of the CD45RA isoform. A typical adult has circulating memory cells with about $25 \times 10^6$ different receptors; in other words, in the process of growing up, one is exposed to about this many different antigens. The immune response that these memory T cells trigger when they encounter their antigen again has the following characteristics:
- There is a more direct pathway to an effective immune response, no longer requiring major innate signals.
- The optimal immune response is produced more quickly.

The activated memory cells in turn activate the adjacent macrophages, which create the inflammation and tissue destruction by releasing cytotoxic substances. The most important mediators are IL-1 and especially TNF. In addition, NO and oxygen radicals are important in destroying the cells loaded with or coated by the target antigen; this frequently includes collateral damage to the surrounding tissue. In patch testing to confirm the diagnosis of allergic contact dermatitis, the resultant Type IV reaction reaches its maximum 3–5 days after allergen exposure. It is important to test potential allergens in a neutral vehicle; otherwise, toxic reactions cannot be separated from DTHR and it is possible to newly sensitize against the allergen or vehicle during the testing process. While this is uncommon, it is of considerable clinical significance.

Type IV allergic reactions or DTHR are distinguished from biologically useful Type IV reactions only by the nature of the target antigen, not by another mechanism. In the skin, many Type IV reactions are directed against haptens, substances that alone are too small to be allergens. Apparently they are bound directly to MHC/HLA molecules and then presented to specific T cells. Type IV reactions can also develop against proteins found in the skin and mucosa.
Pathophysiology of Allergic Reactions

Type IV Reaction I (Delayed-type Hypersensitivity Reaction) (DTHR)

1. Effector phase of contact dermatitis and tuberculin reaction

2. Antigen localization in cell-mediated immune reaction

A. Type IV Reaction

B. CD4 T Cell-mediated Immune Reaction
A. Patch Test Procedure

Patch testing is used to identify agents responsible for allergic contact dermatitis (pp. 30ff, 46f).

**Method.** Standardized test substances are placed in small aluminum wells (Finn chamber) or on patches of filter paper attached to adhesive strips. They are taped onto the back and left on for 48 hours. The reaction is read 20 minutes after removing the tape on day 2, and then again on day 3 and/or 4, as well as on occasion on day 7. The reactions are scored from 0 to 4+ or as irritant (IR). The patient should avoid the use of soap and water on the area during the entire test procedure.

**Problems.** Misleading results can be obtained in a number of ways. Causes of false-positive results include tape irritation and induction of “angry back” syndrome – multiple, not clinically relevant, positive results. In this case, all of the positive items must be tested separately at a later date. Previous exposure to sunlight, UVB irradiation, corticosteroids, and other forms of immunosuppression may produce false-negative results. If patch testing is negative but clinical suspicion is high, the procedure can be repeated or an open use test can be employed. Here the patient applies the suspected substance to the inner aspect of the forearm twice daily for a number of days. A dermatitis is taken as a positive result.

B. Test Substances

Most test substances are mixed in Vaseline, or less often in water. Standard series available in both Europe and the United States include the most common allergens including:

- Metals such as nickel, cobalt, and chromium, and their salts
- Additives used in rubber manufacture such as thiurams and mercapto complexes
- *para*-phenylenediamine, a common dye
- Fragrances and aroma substances
- Components of topical products, including vehicles (wool wax alcohol), preservatives (parabens), or active ingredients (benzoic acid, neomycin)

In each instance, a concentration is determined by testing in normal volunteers and patients so that the number of false-positive and false-negative results is as small as possible.

In addition to the standard test series, there are many specialized test series for special risk groups. Examples include natural latex, fragrances, preservatives, plastics, and rubber additives. The localization of the dermatitis may also give clues as to possible allergens. For example:

- Periorbital—ophthalmological agents, cosmetics, nail polish components
- Hands—skin care products, protective gloves, occupational exposure, jewelry

Series are designed for certain occupations (barber/cosmetician, dentist/dental technician), body regions (perianal), or special situations (atopic dermatitis, photoallergy). Patch testing with nonstandardized products is fraught with problems. If it is tried, the substance must be diluted so that it is nonirritating and the procedure must provide negative results in at least 10 controls.

C. Special Modifications

**Contact urticaria.** Patch testing with latex proteins, proteins from raw vegetables, and enzymes used in baking can be read after 30–60 minutes.

**Atopy patch test.** (1) In patients with atopic dermatitis, aeroallergens such as house dust mites, pollens, or animal hairs may cause not only hives but also dermatitis when applied under patch test conditions. If the patient is extremely sensitive, their dermatitis may flare at other sites. At this point, atopy patch testing must be regarded as not fully established.

**Photo patch test.** (2) If one suspects a photoallergy, the standard photoallergen series is applied in duplicate. One set is irradiated with UVA (5–10 joules/cm²) after 24 hours. Readings are performed as with standard patch testing. Among the frequent photoallergens are chemical UV filters and fragrances.

**Fixed drug reaction.** In this unusual clinical setting, a patch test with the suspected trigger can be applied to the specific skin site where the reaction has occurred.
In vivo Allergy Diagnosis

A. Test Procedure

Read test
- after 48 h
- after 72 h
- (after 7 days)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>(+)</td>
<td>Erythema only</td>
</tr>
<tr>
<td>+</td>
<td>Erythema and infiltrate</td>
</tr>
<tr>
<td>++</td>
<td>Erythema and papules</td>
</tr>
<tr>
<td>+++</td>
<td>Erythema, papules, blisters</td>
</tr>
<tr>
<td>++++</td>
<td>Erythema, blisters, erosions</td>
</tr>
<tr>
<td>IR</td>
<td>Irritant reaction: sharp borders, decrescendo</td>
</tr>
</tbody>
</table>

Immunosuppressive medications

Previous UV irradiation

Tape irritation

Underlying dermatitis

“Angry back”

Reactivity

B. Test Substances

A. Test Procedure

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percent positive</th>
<th>Vehicle</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickelsulfate</td>
<td>12.9 %</td>
<td>Vaseline</td>
<td>5 %</td>
</tr>
<tr>
<td>Fragrance mix</td>
<td>10.5 %</td>
<td></td>
<td>8 %</td>
</tr>
<tr>
<td>Balsam of Peru</td>
<td>7.3 %</td>
<td></td>
<td>25 %</td>
</tr>
<tr>
<td>p-Phenylenediamine</td>
<td>4.5 %</td>
<td></td>
<td>1 %</td>
</tr>
</tbody>
</table>

1. Contact allergen “hit list”

- Aeroallergens, perfumes
- Toothpastes, lipsticks, mouthwashes
- Deodorants/antiperspirants
- Belt buckles, jeans buttons
- Intimate products
- Feet: rubber and leather allergens
- Hair products
- Jewelry
- Clothing
- Cosmetics, nail polishes
- Occupational and hobby allergens, cleaning fluids
- Ankles, shins: medications for stasis dermatitis

2. Typical allergens

B. Test Substances

C. Special Situations

1. Atopy patch test

Patches on back

UV irradiation

2. Photo patch test
Other Ocular Diseases

A. Contact Conjunctivitis

In allergic conjunctival reactions, the lids, conjunctiva, and cornea may be involved. The trigger is contact with an allergen itself (usually a hapten) or in combination with an irritating or toxic substance. Often a contact allergy is triggered by contact lens cleansing or sterilizing solutions or by the long-term use of eye drops, in which case the allergen is usually a preservative.

In allergic reactions, the symptoms tend to appear 48–72 hours after exposure (Type IV reaction). Direct chemical irritation is more common than allergy; signs and symptoms may appear within a few hours if the exposure is extensive.

Clinical features. The periorbital changes include:
- Acute dermatitis with erythema, blisters, edema, and crusting
- Chronic lesions with more crusting, as well as rhagades, lichenification, and dry skin (see D)
The conjunctiva may reveal follicles or papillae, chemosis, and watery or mucoid secretions. Corneal changes may include superficial erosions, subepithelial cloudiness, an inflammatory infiltrate along the corneal border, and, in severe situations, ulcerations or edema. The pruritus can be prominent and most unpleasant.

Therapy. Topical corticosteroids, both as eye drops and for the lids, as well as cold compresses and mild skin care. Mast cell stabilizers, antihistamines and vasoconstrictor eye drops are usually ineffective.

B. Lid Edema

Clinical features. Swelling and erythema of the lids can occur in all forms of allergic conjunctivitis, but are especially common with:
- Allergic rhinoconjunctivitis
- Giant papillary conjunctivitis
- Allergic contact conjunctivitis
The skin of the lid is the thinnest of the entire body and is thus easily damaged or irritated. Systemic Type I reactions such as angioedema also cause lid swelling, but in such cases the itching is not present.

Therapy. Cold compresses

C. Blepharitis

Blepharitis is an inflammation of the lid margins.

Clinical features. The lid margin is inflamed and the lids itch and burn. Patients may complain of a foreign body sensation, increasing tearing, or having their lids glued together in the morning by dried secretions. The lids appear swollen and erythematous, often with crusted secretions on the edge. The conjunctiva are often normal. If corneal ulcers are seen, this suggests secondary bacterial infection. The course tends to be chronic. Etiological agents may include:
- Rosacea
- Seborrheic dermatitis
- Exogenous irritants
- Refractive anomalies
- Bacterial infections of the lash follicles and meibomian glands
- Mite infestation (Demodex folliculorum) of the lash follicles

Therapy. The lid margins should be cleaned with cotton-tipped applicators and diluted baby shampoo; artificial tears should be prescribed. The underlying disease must be treated. If a bacterial infection is confirmed, erythromycin or bacitracin ophthalmic ointment may be helpful.

D. Lid Dermatitis

Lid dermatitis is a chronic process, often seen in patients with atopic dermatitis. It may be associated with contact allergy (A) or secondary to irritation or mechanical trauma. Lichenification is frequent. Typical causes include eye drops, ointments, and cosmetics; preservative agents are often the actual allergens.

Therapy. Avoidance of allergens, cold compresses, brief use of corticosteroid ophthalmic ointments.
**Contact Allergy, Lid Edema, Blepharitis, Lid Dermatitis**

**A. Contact Allergy**
- **Eye drops,** contact lens cleansing solutions
- **Contact allergen**
- Inflammatory infiltrate
- Langerhans cells
- **T cells**
- Neutrophils, macrophages
- Lymphokines, chemokines
- **Edema**
- Increased skin lipids in seborrheic dermatitis
- **Mast cell degranulation**
- **Vasodilatation,** permeability ↑
- **Uncontrolled chronic inflammation**

**B. Lid Edema**
- **Antigen**
- **IgE**
- **Mast cell**
- **Edema**
- **Mast cell degranulation**
- **Fibroblast activation,** lichenification

**C. Blepharitis**
- **Mites,** seborrhea, bacteria, UV radiation, visual disturbances
- **Breakdown of free fatty acids**
- **Increased skin lipids in seborrheic dermatitis**
- **Neutrophilic infiltrate**
- **Inflammation**
- **Tarsus**

**D. Lid Dermatitis**
- **Antigen,** noxious agent
- **Fibroblast activation,** lichenification
- **Uncontrolled chronic inflammation**