



Immune-Mediated Tissue Injury

(Hypersensitivity Reactions)

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INTRODUCTION

Hypersensitivity is synonymous with immune-mediated tissue injury. Hypersensitivity reactions occur in several forms and give rise to numerous conditions including allergies, autoimmune disease, allograft rejection, granulomatous inflammation, and a variety of acute or chronic inflammatory disorders (vasculitis, glomerulonephritis, arthritis, pneumonitis, encephalitis, etc.). While hypersensitivity is usually detrimental, in some cases it represents a normal response to a pathogen (e.g., the granulomatous inflammation of tuberculosis).

Several years ago, Gell and Coombs divided hypersensitivity states into four basic types (1), and this classification remains useful today (Table 1). Type I hypersensitivity reactions result from IgE-dependent degranulation of mast cells or basophils. Type II, or "cytotoxic" hypersensitivity, results from the binding of IgG or IgM antibodies to cell membranes or fixed tissue antigens, causing activation of the complement system. Type III, or "immune-complex" hypersensitivity, results from the formation of immune complexes that precipitate in tissues (or form in situ), also with activation of complement. Type IV, or "cell-mediated" reactions, can be subdivided into two basic types: type IV-A is synonymous with delayed-type hypersensitivity (DTH) and usually occurs in response to soluble antigens; type IV-B results from the direct killing of target cells by cytotoxic T lymphocytes (CTL). Stimulation of cells by anti-receptor autoantibodies (such as the anti-TSH receptor antibodies of Graves' disease) has been designated as type V hypersensitivity by some authors. In addition, there are syndromes caused by massive cytokine release that are not usually referred to as hypersensitivity reactions, although (in accord with the definition) they should be included in that category. Examples are anti-CD3 mAb therapy, superantigen- (superAg) induced diseases (toxic shock syndrome, scalded skin syndrome), and shock caused by endotoxins (gram negative septicemia).

Despite the occurrence of tissue injury, it should be understood that hypersensitivity mechanisms evolved as a means of fighting infectious agents. The mechanisms underlying these hypersensitivity states will be described and some clinical examples will be mentioned. In particular, the important role of cytokines, which is an area where considerable progress has occurred in recent years, will be emphasized.

TYPE I HYPERSENSITIVITY

This type of reaction is also referred to as immediate, anaphylactic, reaginic, or atopic allergy. In type I hypersensitivity, exposure to an allergen (e.g., pollen) results in the production of IgE antibodies (2). IgE antibodies can bind to mast cells and basophils via specific receptors on the Fc portion of IgE. The binding of the antibodies to mast cells has no effect unless the allergen is also present. In this case, an allergen can cross-link two or more IgE molecules on the surface of the mast cell. This cross-linking event triggers degranulation of the mast cell with the release of several mediators (Table 2) (3-6).

Type I or anaphylactic reactions can occur within minutes of the exposure to an allergen. These reactions may be local, e.g., in the skin or the lungs (asthma), or they may be systemic. Reactions range in severity from minor (hay fever, atopic eczema) to potentially lethal (asthma, anaphylactic shock).

The action of the various mediators released during anaphylactic reactions explains the clinical syndromes encountered (Table 2). For example, histamine causes intense bronchial smooth muscle contraction, increased vascular permeability, and increased secretion by nasal, bronchial, and gastric glands (3-6). Leukotrienes C₄, D₄, and E₄ are lipoxygenase derivatives of arachidonic acid and are highly potent mediators of bronchospasm in anaphylaxis (5,6). Chemotactic factors for eosinophils and neutrophils are also released. Mast cells also release prostaglandins through the cyclooxygenase pathway, e.g., prostaglandin PGD₂, which is a potent vasodilator (6,7).

Local anaphylaxis is produced by numerous allergens, such as dust mites, plant pollens, foods, insect venom, latex, and animal dander. Clinically, such reactions can be induced by introducing tiny amounts of allergen into the skin (e.g., skin prick test), a procedure used to test for allergy. A positive skin test is characterized by the wheal-and-flare reaction (local edema surrounded by erythema), occurring within minutes. A late response, manifested as swelling, may also be apparent hours later. A positive skin test usually correlates with the presence of allergen-specific IgE antibodies in serum, as detected with the radioallergosorbent test (RAST).

Systemic anaphylaxis may be a feature of food allergy, insect bites, or may occur after the administration of proteins, hormones, polysaccharides, or drugs (e.g., penicillin) (8). The amount of allergen necessary to cause a systemic reaction is quite small. Minutes after exposure, itching and skin erythema appear, followed by respiratory difficulty with wheezing. This results from a combination of bronchospasm and laryngeal edema. The blood pressure may drop rapidly due to vasodilation, resulting in a state of shock. The prompt injection of epinephrine or a similarly acting drug increases blood pressure and reduces bronchoconstriction (8).

LATE PHASE RESPONSE

The acute response described above is followed 3 to 12 hours later by a late phase response (LPR) (9). The LPR may last several hours or days and is characterized by an inflammatory infiltrate rich in eosinophils. IL-5 (which acts on eosinophils) and other cytokines (see section on cytokines below) are probably important mediators of this reaction. The pulmonary LPR is thought to lead to airway hypersensitivity, an important feature of asthma.

THE REGULATION OF IgE PRODUCTION

The predisposition to type I hypersensitivity correlates strongly with a family history of atopy, as well as high serum levels of IgE. The genetic and environmental factors which determine allergen-specific IgE production are poorly understood. While the MHC class II genotype influences susceptibility to these reactions (10), other genes are also involved.

It is clear that IgE responses are highly T cell dependent, and that the cytokine IL-4 is essential for IgE production. IL-4 is produced by mast cells, basophils, and Th2 lymphocytes. IL-6 also enhances IgE

production, while interferon-gamma (IFN-gamma) is strongly inhibitory. Therefore, type I hypersensitivity reflects a Th2-type immune response, as discussed later.

The properties of the allergens themselves may predispose to IgE immunity. Most allergens are small, highly soluble molecules. The transmucosal presentation of low doses of these antigens may promote a Th2 response. Moreover, some allergens are proteases (3) that may directly stimulate IL-4 production by basophils or mast cells.

TYPE II OR CYTOTOXIC HYPERSENSITIVITY

This form of hypersensitivity results from the binding of antibody to a fixed tissue antigen or a cellular target (11). This occurs in erythroblastosis fetalis where maternal antibodies reactive to blood group antigens, usually Rh, cross the placenta and bind to fetal red cells. In adults, autoantibodies against RBC occur in autoimmune hemolytic anemia. Similarly, antibodies against platelets can induce thrombocytopenia. In SLE, many autoantibodies are found which may induce type II reactions resulting in depletion of RBC, platelets, and leukocytes. In these diseases, activation of complement can lyse cells through the formation of the membrane attack complex (MAC), or may enhance opsonization by the generation of C3b. Phagocytes have Fc receptors and C3b receptors that promote the binding to and elimination of antibody and/or complement-coated cells. Moreover, IgG-coated cells may be lysed by Fc-receptor positive killer cells through the process of antibody-dependent cell-mediated cytotoxicity (ADCC).

An interesting example of type II hypersensitivity is Goodpasture's syndrome (12). In this disease, autoantibodies are formed against a component of basement membranes. Often these autoantibodies bind to both glomerular and pulmonary basement membranes causing acute glomerulonephritis and a hemorrhagic form of pneumonitis. In this case, complement activation initiates a local acute inflammatory reaction due to the release of complement-derived mediators, particularly C3a and C5a (13). Immunofluorescent studies reveal a linear deposition of IgG along the glomerular and/or alveolar basement membrane. The trigger for the formation of these antibodies remains unknown.

In myasthenia gravis, antibodies are formed against the acetylcholine receptor of muscle cells. These antibodies cause muscular weakness by interfering with acetylcholine-mediated stimulation of muscle cells and by activating complement with damage to the motor end-plate (14). Both IgG and C3 can be identified by immunoperoxidase methods at the neuromuscular junction; there is complement-mediated focal lysis of the post-synaptic membrane.

Other examples of type II hypersensitivity diseases are listed in Table 3.

TYPE III OR IMMUNE COMPLEX-MEDIATED HYPERSENSITIVITY

Immune complexes (IC) result when antibodies bind to foreign or self antigens. IC usually form in body fluids, but may also form in situ (e.g., in the glomerular basement membrane). The capacity of IC to cause disease is influenced by their size, by the class of antibody involved, their electrical charge, as well as by other factors (15). Large immune complexes are rapidly cleared by the mononuclear phagocytic system. Small immune complexes may remain in a soluble form and cause little tissue injury. However, IC formed in slight antigen excess tend to precipitate in tissues and cause tissue injury. To a large extent, the ability of IC to cause tissue injury depends on the activation of complement. The prototypic immune complex disease is serum sickness (e.g., a patient injected with a heterologous antiserum, such as horse serum). After a few days, a recipient of such proteins may begin producing antibodies which bind with the foreign proteins and form precipitating IC. These IC precipitate preferentially in the wall of arteries, in glomeruli, in joints, and along serosal membranes. With activation of complement, an acute inflammatory reaction (as described in type II hypersensitivity) occurs at these sites, resulting in vasculitis, glomerulonephritis, arthritis, and serositis.

The Arthus reaction is an example of a local immune complex-mediated reaction which occurs when an antigen is injected into a tissue. In this case, circulating antibodies against the antigen, if present, form IC locally and induce a necrotizing acute vasculitis. A reverse Arthus reaction occurs when antibody is injected locally and antigen is present in the circulation. The tissue lesions are the same in both cases. Unlike type I hypersensitivity, type III reactions occur over a period of hours. For example, the Arthus reaction reaches a peak in 4 to 10 hours.

Systemic lupus erythematosus (SLE) is the best studied disease where immune complexes have been implicated. Antibodies against DNA or other antigens can form immune complexes, which are deposited in several tissues such as glomeruli, blood vessels, joints, and serosal membranes. These immune complexes can activate complement, and thereby induce acute inflammatory reactions resulting in glomerulonephritis, arthritis, vasculitis, and polyserositis (e.g., pericarditis or pleuritis). Immunoglobulins deposited near the dermal-epidermal junction are probably responsible for the frequent skin lesions found in SLE. However, as mentioned above, cytotoxic antibodies also account for some of the clinical manifestations of SLE.

Immune complexes have also been implicated in glomerulonephritis (GN). GN is found in experimental and clinical serum sickness, in SLE, and sometimes follows infection with streptococci (post-streptococcal glomerulonephritis) or other microorganisms. In many cases, GN occurs spontaneously without any identifiable cause. In fact, in most cases of GN, lesions cannot be easily attributed to circulating immune complexes. However, in some cases of GN related, for example, to thyroiditis, syphilis, or hepatitis B, circulating immune complexes and antigens deposited in the glomerular basement membrane can be identified (16).

Another group of diseases where immune complexes have been implicated are the vasculitides. Vasculitis, like glomerulonephritis, is a component of serum sickness and SLE. Two types of vasculitis where immune complexes are believed to be important are hypersensitivity vasculitis and polyarteritis nodosa. Hypersensitivity vasculitis, also called leukocytoclastic vasculitis, may be a part of SLE or another connective tissue disease, or may occur spontaneously as a single disease. Small vessels (arterioles, capillaries, and venules) are affected with a necrotizing inflammatory process. Polymorphs are seen in the walls of the vessels. Most frequently, the skin, mucous membranes, lungs, kidneys, and the brain are involved; however, any tissue in the body may be involved. This type of lesion may be secondary to a drug (e.g., penicillin), to the presence of a foreign protein antigen in the circulation (e.g., a viral protein), or rarely, to the release of an antigen by tumor cells. Presumably, immune complexes are deposited in the walls of small vessels, where they induce type III hypersensitivity responses. In the classical form of polyarteritis nodosa (PAN), larger vessels are involved. Generally, medium-sized muscular arteries display a necrotizing type of inflammatory process. In 25-40% of patients, PAN is associated with hepatitis B viral infection. It appears that circulating antigens, such as hepatitis B surface antigen (HBsAg), give rise to immune complexes which induce vasculitis. The vasculitides are frequently associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA) that may also contribute to the pathogenesis, although their role is still uncertain.

TYPE IV OR CELL-MEDIATED HYPERSENSITIVITY

In this case, T lymphocytes respond against an antigen and usually induce a chronic inflammatory reaction. The tuberculin reaction is a classical example of a type IV-A reaction. The reaction peaks at 24 to 72 hours. For this reason, type IV hypersensitivity is frequently called "delayed-type hypersensitivity" (DTH). These reactions often give rise to granulomatous inflammation, such as in tuberculosis and sarcoidosis. Type IV reactions also appear to be important in autoimmune diseases, such as insulin-dependent diabetes mellitus (where β cells are destroyed by T lymphocytes), and in transplant rejection. Type IV-A hypersensitivity can be divided into the following subtypes: (i) tuberculin-type hypersensitivity (equivalent to DTH); (ii) granulomatous inflammation (requires at least two weeks to occur); and (iii) contact hypersensitivity (e.g., poison ivy reaction).

In DTH, soluble protein antigens are processed by macrophages or dendritic cells and presented to Th1 lymphocytes in the context of class II MHC molecules. The Th1 cells secrete IL-2, IFN- γ , and TNF- β (17-19). IFN- γ is a particularly important mediator of this reaction through its ability to activate macrophages (20). The tissue reaction is characterized by a mononuclear cell infiltrate with or without granuloma formation. Granulomatous inflammation is not a special type, but occurs when DTH is prolonged for more than two weeks.

Contact hypersensitivity is typically an inflammatory response limited to the epidermis. In this case, T cells react to modified epidermal antigens that are probably presented by Langerhans cells. This occurs when some small molecules act as haptens by binding to normal proteins following skin contact. Common molecules in this group include the allergen of poison ivy (pentadecacatechol), nickel, chemicals found in rubber, and chromate (3). Dinitrochlorobenzene (DNCB) will sensitize almost all individuals in this way.

Type IV-B reactions are an entirely different group, where CTLs directly kill target cells. This may occur in viral infections (e.g., chronic active hepatitis), in allograft rejection, in graft-vs.-host disease, and probably in some organ-specific autoimmune diseases.

CYTOKINE EFFECTS IN HYPERSENSITIVITY

Studies of T helper (Th) clones in mice and humans have revealed the existence of three main types of clones based on patterns of cytokine production: Th1 clones secrete IL-2, IFN- γ , and TNF- β (lymphotoxin); Th2 clones secrete IL-4, IL-5, IL-6, IL-10, and IL-13; and Th0 clones secrete the cytokines produced by both Th1 and Th2 clones (17-19,21). There are species differences in the cytokine expression profile of these clones. For example, while murine Th1 clones do not produce IL-6 and IL-10, these two cytokines are produced by human Th1 clones (but usually in lower amounts than human Th2 clones) (18,19). The existence of T cells with similar cytokine production patterns in vivo was confirmed primarily by the study of parasitic diseases and allergic diseases. In mice, resistance to several (but not all) parasitic diseases correlates with DTH and strong Th1 responses, while humoral immunity (particularly IgE production) correlates with Th2 responses (18-24). This appears to be the case in humans as well. Notably, Romagnani and his colleagues (18,19,25) found that most T cell clones specific for allergens (e.g., *Toxocara canis* excretory/secretory [TES] antigens) exhibited a Th2-like profile of cytokine production. However, the great majority of T cell clones specific for purified protein derivative (PPD) from *Mycobacterium tuberculosis* derived from these same donors had a Th1 cytokine profile. In tissues, Th1 and Th2 patterns of cytokine production have been documented based on cytokine mRNA expression (in situ hybridization, RT-PCR), and other techniques (26-28). Cytokine effects in type I and type IV hypersensitivity are summarized in Fig. 1 and 2, respectively.

Based on numerous studies, the current concept is that virgin T cells produce only IL-2. They can then mature, first into Th0, and subsequently into Th1 or Th2 clones following several rounds of stimulation with antigen. Th1 clones mediate DTH responses and have cytotoxic potential, but only enhance immunoglobulin secretion (IgM, IgG, IgA, but not IgE) at low T cell:B cell ratios (18,19). Th1 cells can kill target cells by direct contact through the Fas ligand (29), or by secreting TNF (alpha or β) (30). Th2 clones are more effective than Th1 clones at promoting immunoglobulin secretion and are required for IgE production. They do not promote DTH and have no cytotoxic potential. Th0 cells, as would be expected, have intermediate effects.

Th1 and Th2 clones are mutually inhibitory. Th1-derived IFN- γ inhibits the proliferation of Th2 cells, while Th2-derived IL-4 (and IL-10 in mice) can inhibit cytokine production by Th1 clones (18,19,21,31). The factors which influence differentiation along the Th1 or the Th2 pathways are not fully understood. IL-2 is the primary growth factor of Th1 cells, while IL-2 and IL-4 stimulate growth of Th2 cells. Studies performed in vitro suggest that IL-1 and IL-4 are required for the development of human Th2 clones, whereas IL-12, IFN- α , TGF- β , and IFN- γ promote Th1 differentiation (18,31). Note that some of these cytokines

can be produced by both T and non-T cell types. Macrophages can produce IL-1, IL-12, IFN-alpha, and TGF- β (also IL-10, but in man this cytokine inhibits both Th1 and Th2 cells) (18,19). NK cells produce IFN-gamma, a response enhanced by IL-12 (32,33). Mast cells and basophils can produce IL-4 and other cytokines (34). In vivo, it is likely that secretion of cytokines by these non-T cell types influences Th1 and Th2 differentiation. Moreover, there is evidence that gamma* T cells may respond to various antigens by producing either IFN-gamma or IL-4, and thereby promote differentiation of either Th1 or Th2 (35).

CYTOKINES IN SPECIFIC TYPES OF HYPERSENSITIVITY

A detailed discussion of the many cytokine effects reported in hypersensitivity diseases is beyond the scope of this review, but some well recognized patterns will be mentioned.

Allergic Disorders

The role of IL-4 in stimulating IgE production has already been mentioned. However, other cytokines are also involved in the pathogenesis of type I hypersensitivity (Fig. 1). This is best illustrated by studies of allergic asthma (6,9,26,27). Detectable levels of mRNA for TNF-alpha, IL-1, IL-3, IL-4, IL-5, and GM-CSF have been reported in biopsies or bronchoalveolar lavage (BAL) cells. IL-2 and IL-6 have also been detected, at least at the protein level (27). Cytokine producer cells may include T cells (Th2), basophils, mast cells, macrophages, eosinophils, and epithelial cells. IL-5 is overproduced and may play a particularly important role by increasing the number and activity of eosinophils (36,37). Eosinophilic infiltration is a characteristic feature of asthma and these cells can release several toxic mediators (eosinophilic cationic protein, eosinophil peroxidase, major basic protein, etc.). In this way, as mentioned earlier, cytokines produce a late phase response that is probably responsible for bronchial hypersensitivity.

Interestingly, asthmatics can be divided into steroid sensitive (SS) or steroid resistant (SR) groups, based on the response to glucocorticoids (38). In SS patients, prednisone therapy induces a depression of IL-4 and IL-5 and an increase of IFN-gamma (at least at the mRNA level), while in SR patients, IL-4 and IL-5 are unchanged and IFN-gamma is decreased. Thus, positive or negative responses to therapy appear to relate to the cytokines produced.

Cytokine Production in DTH

In DTH, there is a complex interaction between CD4⁺ T cells (Th1) and macrophages which is mediated in large part by cytokines (Fig. 2). In the human, this is well illustrated by studies of leprosy. The immune response to *Mycobacterium leprae* varies widely, from the "tuberculoid" leprosy pattern with potent DTH, granulomas, and low numbers of organisms in tissues, to the "lepromatous" pattern with weak or suppressed DTH and numerous organisms. Examination of the tuberculoid lesions reveals high mRNA expression of IL-2, IFN-gamma and TNF- β in tuberculous leprosy, with low expression of IL-4, IL-5, and IL-10 (28,39,40). Conversely, in patients with lepromatous leprosy, there is low expression of IL-2, IFN-gamma, and TNF- β , but high expression of IL-4, IL-5, and IL-10. Therefore, while the tuberculoid type, which is associated with the better prognosis, correlates with a Th1 response, the lepromatous type results in a Th2 response. This type of polarity in the response to intracellular organisms or parasites has been documented in other diseases as well (for reviews, see references 18,23,39). Presumably, DTH results in high IFN-gamma production; this cytokine activates macrophages which can then eliminate these organisms. In some infectious diseases, however, Th2 responses may be more protective than Th1 responses, probably because antibodies are involved. For example, the response to gut-dwelling helminths is clearly a Th2 type, with high IL-4 and IL-5 secretion, high serum IgE, and eosinophilia (18,41). However, the degree of protection afforded by this Th2 response is unclear.

Cytokines in Autoimmune Diseases

Our studies (42) and those of others (43,44) do not reveal a clear-cut Th1 or Th2 cytokine pattern in systemic lupus erythematosus (SLE). Overexpression of IFN-gamma, IL-10, and IL-1 β mRNA in the lymph nodes of lupus-prone mice were found, but there were no abnormality in IL-4, IL-5, and IL-6 expression. Similar results have been reported in SLE patients, except that IL-6 was also elevated (43,44). This is surprising, since this disease is characterized by B cell hyperactivity and hypergammaglobulinemia, a pattern that seems more consistent with a Th2 response. However, it should be remembered that Th1 and Th0 cells (which both produce IFN-gamma) can enhance antibody production, at least at low T cell:B cell ratios.

Th1 responses, manifested as DTH, are thought to play an important role in organ-specific autoimmune diseases (45). This has been clearly demonstrated in experimental allergic encephalomyelitis in mice (45-48) and is probably also the case in spontaneous autoimmune diabetes in NOD mice (45,49). In humans, there is evidence of Th1 responses in autoimmune thyroid disease and multiple sclerosis (18).

SYNDROMES CHARACTERIZED BY MASSIVE CYTOKINE RELEASE

In some bacterial infections, cytokine release can cause severe and potentially lethal clinical manifestations. This may be due to the production of exotoxins with superAg properties (staphylococcal or streptococcal) or to endotoxins (as in gram-negative septicemia). Massive cytokine release is also a complication of anti-CD3 mAb therapy due to activation of T cells (50,51).

SuperAg-Induced Diseases

SuperAgs are molecules with the remarkable ability to activate a large number of T cells (5-30%) by binding to specific TCR-V β elements and simultaneously (at another site) to MHC class II molecules. Formation of this molecular bridge results in T cell activation and release of multiple cytokines that may be produced either by the T cells (IL-2, IFN-gamma, TNF- β , etc.) or the macrophages (TNF-alpha, IL-1, IL-12, etc.). Since a large number of cells are activated rapidly, there may be an abrupt release of large amounts of cytokines, with serious clinical manifestations. The best example of a superAg-induced disease is toxic shock syndrome (TSS) that affects primarily (but not solely) menstrual age women. This is a systemic disorder with fever, hypotension, multi-organ failure, a musculo-papular erythematous rash with desquamation, myalgia, and thrombocytopenia (52-54). Menstruation-related TSS is usually caused by toxic shock syndrome toxin-1 (TSST-1), a product of *Staphylococcus aureus* that may grow in the vagina. Non-menstruation related TSS can also be caused by TSST-1 (50% of cases) or by other toxins, e.g., staphylococcal enterotoxin B (SEB) or enterotoxin C (SEC1-3). TSST-1 binds to T cells expressing V β 2, but SEB and SECs bind to several other TCR-V β elements (52,55).

Kawasaki disease is very similar to TSS, and is thought by some investigators to be caused by a superAg, perhaps of staphylococcal or streptococcal origin (53,56). Other diseases now suspected of being caused by superAgs include scarlet fever (from streptococcal pyrogenic exotoxins), scalded-skin syndrome (from staphylococcal exfoliative toxins), and some forms of staphylococcal food poisoning (52-54). The list of microbial superAgs is constantly growing, and it is likely that many other disease associations will be documented.

The pathophysiology of TSS is not fully understood, but the disease is T cell dependent, with massive secretion of TNF-alpha. Although this cytokine is primarily a macrophage product, TNF-alpha or TNF- β can also be produced by T cells. Perhaps T cell cytokines drive macrophages to produce TNF. In any case, TNF-alpha has many systemic effects that are consistent with the clinical manifestations of TSS (see TNF-alpha and

Shock, below). It is likely that other cytokines also contribute (IL-1, IL-2, IFN-gamma, etc.).

CD3 mAb-Induced Cytokine Release

It is noteworthy that when patients are treated with anti-CD3 mAb for immunosuppressive purposes, there is an initial activation of T cells and a massive release of cytokines. This is associated with a TSS-like disease, although it is transient and less severe (50,51). There is a sharp rise in TNF-alpha in serum, but IL-2 and IFN-gamma are also elevated. This reaction is not usually life-threatening and can be prevented with corticosteroids.

Endotoxic Shock

Septic shock is one of the most common causes of death in intensive care units and results from the spread of bacteria in the blood. However, many of the clinical manifestations are caused by cytokines. The majority of cases of endotoxic shock are caused by endotoxin-producing gram-negative bacilli. Endotoxins are lipopolysaccharides that can activate macrophages and induce the production of monokines, particularly TNF-alpha and IL-1 (57,58). Other mediators involved include IL-6, IL-8, nitric oxide, platelet activating factor, prostaglandins, leukotrienes, complement components, and kinins (58). The result is shock (vasodilation, hypotension), endothelial injury, disseminated intravascular coagulation, and multiple organ failure, with death being a common outcome. TNF-alpha appears to play a key role, and this condition can be attenuated or prevented with anti-TNF-alpha antibody treatment (58,59). In fact, the toxicity of TNF-alpha closely mimics the clinical features of endotoxemia.

TNF-alpha and Shock

Studies have shown that the predominant manifestation of the acute release of large amounts of TNF-alpha in the circulation is shock (58,59). TNF-alpha causes a decrease in peripheral vascular resistance, decreased cardiac output, and capillary leakage. TNF-alpha acts on endothelial cells to induce procoagulant activity, a feature that promotes DIC, and to increase nitric oxide synthesis, a mediator that decreases vascular tone and cardiac function. IL-1 acts synergistically with TNF-alpha in these effects (59). Moreover, TNF-alpha is highly toxic to the lungs and contributes to the development of adult respiratory distress syndrome (60).

CONCLUSION

The hypersensitivity reactions represent a complex and diverse group of disorders where immune mechanisms are responsible for tissue injury. These reactions are relevant to many diseases: allergic diseases, autoimmune diseases, transplant rejection, chronic inflammatory disorders, infectious diseases, and some forms of shock. The prevention, diagnosis, and treatment of these diseases depend on a sound understanding of their immunopathogenesis and particularly of the role of the mediators involved.

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