Autoimmune Kidney Injury

Autoimmunity and autoimmune disease

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Introduction

A disease is defined as autoimmune if the tissue damage is caused by an adaptive immune response to self-antigen. Development of the disease by transferring the active component of the immune response to an appropriate recipient is the best proof that the disease is caused by autoimmunity.

The body contains large numbers of potentially autoreactive B and T cells, although there are a variety of mechanisms operating to establish self-tolerance during lymphocyte development. This is particularly true for thymic T cells that are not deleted by self-epitopes. The presence of autoreactive B cells in the normal population is well demonstrated by the development of autoantibodies when autoantigens are injected with adjuvants in normal animals (e.g. anti-thyroglobulin). Existence of autoreactive T cells in normal individuals is demonstrated by the production of autoimmune lines of T cells when normal circulating T cells are stimulated by the appropriate autoantigen (e.g. myelin basic protein) and interleukin-2.

Autoimmune disease can be classified as organ specific, when the response is primarily against antigens localized to particular organs or as non-organ specific, when the response is directed against widespread antigens. Hashimoto’s thyroiditis and SLE represent the extremes of autoimmune disease spectrum. In organ specific diseases, the thyroid, adrenals, stomach, and pancreas are the usual target organs. The non-organ specific diseases, which include the rheumatic disorders, characteristically involve the skin, kidney, brain, lungs, joints, and muscles [1].

Pathogenetic aspects

When a disease is found in association with autoimmune reactions, it is most probable that autoimmunity exerts a pathogenic role and produces the disease lesions. However, there are two other possible interferences.

(i) Development of autoantibodies is attributed to tissue damage (trauma or infection) produced by the disease (e.g. cardiac autoantibodies after myocardial infarction).

(ii) There is a factor causing both the autoimmunity and the lesions.

Evidence supporting the pathogenic role of the autoimmune process in producing the lesions is:

- Induction of autoimmunity in experimental animals that produces organ specific disease in certain organs, e.g. anti-basement membrane antibodies from a patient’s kidney, who died with Goodpasture’s disease, transferred to a monkey which subsequently died with glomerulonephritis.

- The natural experiment of transferring autoimmune disease from mother to fetus with autoantibodies passing the placenta and subsequent disappearance of the disease in the newborn by catabolization of the maternal antibodies or by plasmapheresis, is one of the best proofs that particular autoantibodies exert pathogenic effects (e.g. neonatal lupus).

- The pathogenic role of immune complexes in systemic autoimmunity: in SLE immune complexes containing DNA and antibody are deposited in the kidney, skin, joints, and choroid plexus of the patient and produce type III hypersensitivity reactions, tissue damage and autoimmune disease. Individuals deficient of the early classical pathway complement, component are susceptible to the development of SLE since clearance of immune complexes is inadequate [1].

The development and expression of autoimmune disease can be influenced by variable factors

Genetic predispositions, environmental factors, the effect of sex hormones and stress may all contribute to the development of autoimmune diseases.
Autoimmunity and autoimmune disease

Genetic factors

Evidence of genetic factors operating in autoimmune disease include: (i) a clear familial incidence as proven from studies of identical and non-identical twins [2], (ii) a tendency for the disease to be linked with particular HLA specificities, and (iii) the presence of certain genes that predispose individuals to develop autoimmunity and other that determine the antigen or antigens involved, as shown from animal studies.

Environmental factors

Molecular mimicry by cross-reactive microbial antigens can stimulate autoreactive B and T cells and so, influences the development of autoimmunity (break tolerance). When naive autoreactive T cells recognize cryptic self-epitopes they cannot be activated because the antigen is only presented at low concentrations on ‘professional’ APCs or it is presented on ‘non-professional’ APCs, e.g. pancreatic β-islets cells or salivary gland epithelial cells [3]. Infection with a microbe bearing antigens that cross-react with the cryptic self-epitopes will sufficiently load the professional APCs and so, activate the naive autoreactive T cells. Once activated, these T cells show a higher avidity for the self-epitope-non-professional APCs complex, without co-stimulatory signal, due to upregulation of accessory adhesion molecules [1].

Many autoreactive B cells are inactive either because the CD4 helper T cells are tolerant at lower concentrations of autoantigens or because they only recognize cryptic epitopes. When a cross-reacting microbial antigen bears a new carrier epitope to which T cells are not tolerant, these inactive B cells can be switched on. The activated B cells now present the autoantigens to normally resting autoreactive T cells, which will then act as helpers even after clearance of the foreign antigen.

The presence of an autoantibody will not produce autoimmune disease unless there is availability of the autoantigen to bind the autoantibody. This availability can be affected by environmental factors such as tissue injury. For example, in Goodpasture’s disease there are antibodies against type IV collagen of the basement membrane, which is a common component of glomerular, alveolar and cochlear basement membranes. Although all patients develop glomerulonephritis, only 40% develop pulmonary haemorrhage and none become deaf. Alveolar basement membrane becomes accessible to circulating autoantibodies when there is injury to endothelial lining of pulmonary capillaries such as damage caused by cigarette smoking [4].

Stress

Several diseases, including autoimmune ones, have been associated with psychological factors, as has been demonstrated with variable results by psychosocial interventions. Evidence from the literature concerning the influence of minor and major stress factors reveals that major life events and chronic minor stress are associated with the onset of rheumatic diseases and in some of them, stress may be a provoking factor for genetically predisposed individuals [5].

Sex hormones

The effects of sex hormones in susceptibility to autoimmunity have been studied extensively. Androgens and oestrogens can influence the susceptibility and the course of rheumatic diseases. More specifically, androgens in a concentration-independent way suppress cellular and humoral immunity while oestrogen metabolites have been shown to increase B-cell differentiation and activate T cells. Endogenous oestrogen fluctuations (e.g. in pregnancy) and exogenous oestrogens for replacement therapy or contraception enhance susceptibility to autoimmune diseases and may lead to aggravation during the course of the disease [6].

Autoimmune kidney injury

The major function of the glomeruli is the filtration of plasma and the endothelium lining glomerular capillaries is fenestrated to allow access of plasma to the basement membrane, which is acting as a barrier. As autoreactive cells and autoantibodies are carried into the plasma, the kidney becomes a major target for autoimmunity due to the great availability/accessibility of its autoantigens. Immune renal injury can be analysed in the initiating event (autoimmune phenomenon) and the processes that mediate tissue injury. The initiating event is further characterized by the site of the immune interaction (within the kidney or the circulation) and by the type of the immune reaction (humoral or cell mediated).

After the initiating event, immune-mediated tissue injury is caused by soluble/humoral and cellular mediators [7,8]. Humoral mediators are derived from circulating precursor proteins (e.g. complement and coagulation proteins) or through the de novo synthesis of peptides or lipids (e.g. vasoactive peptides, cytokines, growth factors, and eicosanoids). Cellular mediators include neutrophils, eosinophils, monocytes, macrophages, T cells, and platelets.

Interaction between humoral and cellular mediators leads to cell activation and release of local factors that enhance tissue injury (e.g. toxic oxygen radicals, membrane bound procoagulants, cationic proteins, enzymes, growth factors, and interleukins). Cell activation also induces expression of cell-surface molecules that promote their adhesion to vascular endothelium and their migration and localization within sites of the tissue injury.

After the initiating immune events and subsequent inflammatory tissue injury, ongoing damage is caused by non-immune, non-inflammatory factors such as...
hypertension, vascular disease, atherosclerosis of the small vessels or maladaptive responses of the kidney to the loss of functional nephrons. These factors may be important determinants of the outcome and prognosis of an immune-mediated kidney injury [8].

Immunopathogenic mechanisms of kidney injury

In Table 1 representative autoimmune diseases with their renal pathology are depicted.

Anti-tissue antibody-mediated disease

Both insoluble components of the extracellular matrix (e.g. basement membrane) and soluble components of the cells closely related to the matrix may act as intrinsic antigens. Circulating antibodies derived from an expanded autoreactive B-cell clone bind to the glomerular antigens and cause structural and/or functional changes of the glomerular circulation. In Goodpasture’s syndrome, antibodies formed against the α3 chain of basement membrane type IV collagen, bind to the basement membrane of renal glomeruli and, in some cases, to the basement membrane of the pulmonary alveoli, causing a rapidly fatal disease, if untreated. Glomerular immunofluorescence reveals a linear deposition of the autoantibodies along the glomerular basement membrane. The antibody causes local activation of cells bearing Fc receptors, complement activation and influx of neutrophils [4,9].

In situ immune complex-mediated disease

Circulating substances, both endogenous and exogenous, with a biochemical or immunological affinity for glomerular structures (capillary wall or mesangium) bind on these structures and form ‘planted’ antigens. Such substances include certain drugs, plant lectins, cationized plasma proteins, aggregated immunoglobulins, and deoxyribonucleic acid. The reaction with a circulating antibody can give rise to the immunohistochemical alterations discussed above [8].

Circulating immune complex disease

Immune complexes are produced whenever there is an antibody response to a soluble antigen. Normally, such complexes cause little tissue damage because they are cleared efficiently by red blood cells bearing complement receptors and by phagocytes of the mononuclear phagocytic system that have both complement and Fc receptors.

Failure of this system can occur in three circumstances [4].

(i) Injection of large amounts of antigen produces large amounts of immune complexes that overwhelm the normal clearance mechanisms (e.g. serum sickness, a transient disease lasting only until the immune complexes have been cleared).

(ii) Persistent endogenous release of antigen in association with a strong antibody response causes widespread immune complex injury to small blood vessels in organs (e.g. kidney and skin injury in bacterial endocarditis).

(iii) A wide range of autoantibodies is produced to common cellular components in systemic autoimmune diseases. In SLE the main antigens are three intracellular nucleoprotein particles—the nucleosome, the spliceosome, and a small cytoplasmic nucleoprotein complex, so large quantities of antigen are available in all the nucleated cells in the body. Large numbers of small immune complexes are continuously produced and are deposited in the walls of small blood vessels (and in the basement membrane) of the glomerulus, joints, and other organs. Subsequent activation of phagocytic cells leads to tissue damage, release of more nucleoprotein complexes and further formation of immune complexes. Once deposited in glomeruli, immune complexes evoke local inflammatory and functional changes, which are largely independent of complement or polymorphonuclear leucocytes. Infiltrating monocytes may play a more critical role in glomerular damage. Antigens in immune complexes may be

<table>
<thead>
<tr>
<th>Clinical entity</th>
<th>Goodpasture’s syndrome</th>
<th>SLE nephritis</th>
<th>Cryoglobulinaemia</th>
<th>Vasculitides</th>
<th>Wegener</th>
<th>Microscopic</th>
<th>Antiphospholipid syndrome</th>
<th>Sjögren’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenetic category</td>
<td>Autoantibody mediated</td>
<td>Immune complexes</td>
<td>Pauci-immune cellular immunity</td>
<td>Antibody mediated thrombotic vasculopathy</td>
<td>Cellular immunity *immune complexes</td>
<td></td>
<td></td>
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<tr>
<td>Serologic marker</td>
<td>Anti-GBM antibody</td>
<td>Anti-ds-DNA mixed cryoglobulinaemia</td>
<td>ANCA</td>
<td>Anti-cardiolipin, lupus anticoagulant, anti-β2GPI</td>
<td>Anti-Ro/SSA, anti-La/SSB, *cryoglobulins</td>
<td></td>
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<tr>
<td>Complement (C)</td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>*Low</td>
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<td></td>
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</tr>
<tr>
<td>Tissue immunofluorescence</td>
<td>Linear Igs and C</td>
<td>Granular Igs and C</td>
<td>Absent or sparse Igs and C</td>
<td>Absent or sparse Igs and C</td>
<td>*IgM and C3</td>
<td></td>
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</tbody>
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*Immune complex mediated renal pathology inducing vasculitis-glomerulonephritis.
†Immunoglobulins.
exogenous, e.g., derived from infectious agents such as bacteria, viruses or parasites (infective endocarditis, hepatitis B, and malaria), or endogenous including DNA, thyroglobulin, autologous immunoglobulins, renal tubule antigens, and tumor-specific or tumor-associated antigens.

There is no immunochemical relationship between the autoantigen and the renal structures in this mechanism of kidney injury.

**Cell-mediated immunity in glomerular and tubulointerstitial injury**

Activated T cells, specific, for self-peptide–MHC complexes, can cause local inflammation by activating macrophages or by direct cell damage. Extensive infiltration by T lymphocytes and activated macrophages are characteristic of the affected tissues.

It is much more difficult to demonstrate the existence of autoreactive T cells than the presence of autoantibodies for two reasons: (i) it is impossible to transfer disease to experimental animals by injection of autoreactive human T cells because T cell recognition is MHC restricted and animals and humans have different MHC alleles and (ii) it is difficult to identify the antigen recognized by a T cell.

In a variety of inflammatory autoimmune diseases, self-antigens are presented to Th1 cells by MHC class II molecules, so the T cells are triggered to release lymphokines that initiate local inflammation with accumulation of polymorphonuclear leukocytes and macrophages and cause tissue injury.

- Macrophages probably damage tissues by releasing cytokines (IL-1, TNF, IL-6), growth factors (transforming growth factor, platelet-derived growth factor), proteolytic enzymes, and reactive oxygen species.
- T cells recognize antigens presented in association with class II MHC molecules and subsequently destroy them directly. In addition, T cells participate in injury causing infiltration of tissue by other cells, such as macrophages. T cells may also directly promote fibrogenesis.

Other autoimmune diseases are caused by presentation of self-peptide–MHC class I complexes to autoreactive CD8 T cells.

Glomerular diseases that lack the typical hallmarks of antibody-mediated disease, such as immunoglobulin deposits, are candidates for cell-mediated mechanisms [8].

Chronic tubulointerstitial kidney injury (Sjögren’s syndrome) and pauci-immune form of glomerulonephritis (Wegener’s granulomatosis and other forms of vasculitis) [10] are examples of renal injury caused by primarily Th1 cellular immune mechanisms.

**Conclusions**

In the last decades studies of experimental animal models and kidney tissues from patients with autoimmune disorders have provided a better understanding of the many possible ways by which the immune system can cause renal injury.

Humoral immune reactions (autoantibody mediated) with either soluble-circulating (exogenous or endogenous) or tissue fixed (native or planted) antigens lead to antigen–antibody complex formation in the glomerulus or the tubulointerstitium thereby initiating an immune attack. The subsequent tissue damage is produced by the generated activation of humoral (complement or and coagulation cascades) or cellular (neutrophils, monocytes, macrophages) systems.

Cellular immune mechanisms, primarily Th1, operate in the chronic tubulointerstitial kidney injury (Sjögren’s syndrome) as well as in the pauci-immune forms of glomerulonephritis observed in Wegener’s granulomatosis and other forms of vasculitis.

**References**