Toxin-induced immunological renal disease

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Introduction

The last years have provided insight as to how lymphocytes respond to antigen or xenobiotics, and have increased our understanding of the pathophysiology of renal diseases. This points out new clues on the mechanisms by which chemically-induced immune response trigger immune nephropathies. We will describe the T-cell subsets including Th1 and Th2 cells that may be implicated in renal inflammation. The role of Th1 and Th2 CD4+ T-cell subsets in the development of some nephropathies will be debated. Then, we will evoke the mechanism by which a drug or its metabolites may trigger autoimmunity or hypersensitivity reactions. Third, we will report nephropathies induced by xenobiotics in patients, emphasizing the possible underlying mechanisms. Fourth, we will focus on some experimental models of chemical-induced systemic autoimmune diseases that illustrate mechanisms described before. Finally, we will discuss recent insights from these models onto the genetic control of susceptibility to drug-induced immunopathology. This will allow us to introduce the impact of genetic studies in our understanding of the pathogenesis of immune nephropathies, which undoubtedly in the future will shed new light on toxin-induced nephropathies.

T cell-subsets and their role in the development of nephropathies

Characterization of T-cell subsets

CD4+ T-lymphocytes are heterogeneous in terms of production of cytokines and functions [1-4]. Table 1 indicates some characteristics of these subsets. Th1 cells secrete interleukin (IL)-2, IFN-γ and lymphotoxin, which explains their role in activating macrophages and cytotoxic cells and therefore in cell-mediated immune responses. Th1 cells also help B-cells in the production of some isotypes: complement-fixing IgG2a in mice and IgG2b in rats. Th1 cells are responsible for delayed hypersensitivity reactions and are implicated in inflammatory processes with the recruitment of macrophages and neutrophils in the inflamed tissues. Th2 cells produce IL-4, IL-5, IL-6, IL-13 and IL-10 (in mice), promote IgE and IgG1 switch (in rats and mice) - IgE and IgG4 in humans; they activate eosinophils and mast cells. Th2 cells play an important role in the elimination of extracellular parasites such as helminths. In some situations, regulatory properties have been attributed to Th2 cells, owing to their capacity to produce the immunosuppressive cytokine IL-10 (in mice) and to the antagonistic effect of Th2 cytokines on the differentiation of Th1 and Th17 lymphocytes. This latter subset produces IL-17 and is involved in chronic inflammation. Th2 cells are clearly responsible for eosinophil- and mast-cell-mediated inflammation that characterizes particularly allergic asthma. Th1 and Th2-cells express different chemokine receptors [5] and display lineage specific transcription factors. c-maf, NIP-45 and GATA-3 characterize Th2 cells and control Il4 and Il5 gene transcription while T-bet is expressed in Th1 cells and is essential for IFN-γ expression (reviewed in [6]). The transcription factor RORγ controls IL-17 production by Th17 cells [7]. Regulatory T cells (Treg) include several types of natural and antigen-induced T

<table>
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<th>T-cell subset</th>
<th>Cytokines produced</th>
<th>Lineage-specific transcription factor</th>
<th>Functions</th>
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<tbody>
<tr>
<td>Th1</td>
<td>IFN-γ, LT, TNF-α</td>
<td>T-bet</td>
<td>Eradication of intracellular pathogens, virus … Help to CD8+ T-cells, to B-cells (IgG2a, IgG3 in mice) Autoimmunity type 1 diabetes</td>
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<tr>
<td>Th17</td>
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<td>Eradication of pathogens Chronic inflammation</td>
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<td>Th2</td>
<td>IL-4, IL-5, IL-13, IL-6, IL-10</td>
<td>GATA-3, c-maf, NIP-45</td>
<td>Elimination of parasites B-cell help IgE, IgG1 Allergy (asthma)</td>
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<td>Natural Treg</td>
<td>IL-10, TGF-β ? *</td>
<td>FOXp3</td>
<td>Regulation of Th1, Th17 and Th2 cells</td>
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LT = lymphotoxin. * How regulatory T-cells control the other T-cell subsets in vivo remains unclear, especially with respect to the role of IL-10 and TGF-β.